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(54) **Piperazine derivatives as Tachykinin antagonists**

Piperazinderivate als Tachykinin Antagonisten

Dérivés de pipérazine en tant qu'antagonistes de Tachykinine

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Description

[0001] The present invention relates to new piperazine derivatives and a pharmaceutically acceptable salt thereof.

[0002] More particularly, it relates to new piperazine derivatives and a pharmaceutically acceptable salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like, to a process for preparation thereof, to a pharmaceutical composition comprising the same, and to a use of the same as a medicament.

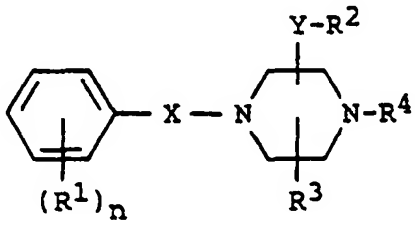
[0003] Accordingly, one object of the present invention is to provide new and useful piperazine derivatives and a pharmaceutically acceptable salt thereof which have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism, Neurokinin B antagonism, and the like.

[0004] Another object of the present invention is to provide a process for the preparation of said piperazine derivatives and a salt thereof.

[0005] A further object of the present invention is to provide a pharmaceutical composition comprising, as an active ingredient, said piperazine derivatives and a pharmaceutically acceptable salt thereof.

[0006] Still further object of the present invention is to provide said piperazine derivatives or a pharmaceutically acceptable salt thereof as a medicament, in particular as Tachykinin antagonist, especially Substance P antagonist, Neurokinin A antagonist or Neurokinin B antagonist. Further, an object of the invention is to provide a use of said derivative for the manufacture of a medicament for treating or preventing Tachykinin-mediated diseases, for example, respiratory diseases such as asthma, bronchitis, rhinitis, cough, expectoration, and the like; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis, and the like; inflammatory diseases such as rheumatoid arthritis, osteoarthritis, and the like; pains or aches (e.g., migraine, headache, toothache, cancerous pain, back pain, etc.); and the like in human being or animals.

[0007] The object compound of the present invention can be represented by the following general formula (I):



(I)

wherein
X, Y, R^1, R^2, R^3, R^4, and n are defined as in claim 1,
or its pharmaceutically acceptable salt.

[0008] GB-A-2,230,262 discloses 2-substituted N,N-ditrimethoxybenzoyl piperazine compounds having an PAF-antagonistic acivity, an antagonistic effect on the passive cutaneous anaphylaxy reaction and a reducing effect on immun bronchospasm induced by antigen injection. The compounds disclosed in said document bear phenyl groups as substituents corresponding to R^2 in the compounds of the present invention.

[0009] EP-A-0 411 150 discloses indole derivatives having an inhibitory effect against superoxide radicals and antialbuminuria activity in Masugi nephritis.

[0010] GB-A-2 271 774 discloses 1,4-piperazine derivatives which are useful as tachykinin receptor antagonists.

[0011] WO 95/00497 discloses inhibitors of farnesyl-protein transferase and inhibitors of the farnesylation of the oncogene protein Ras. This document is a document according to Article 54 (3) EPC.

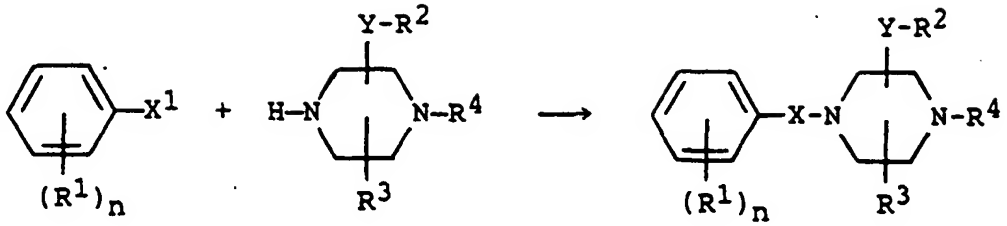
[0012] EP-A-0 368 670 describes trisubstituted piperazine compounds which are useful as PAF antagonists. Said compounds do not have a heterocyclic substituent corresponding to R^2 of the compounds of the present invention.

[0013] WO 92/20661 discloses N,N-diacylpiperazines which have an angiotensin II-antagonistic activity and which are selective for the type 2 (AT_2) subtype. Further, they have antidopaminergic properites, tachykinin receptor antagonistic activity and are calcium channel blockers. The compounds do not have a heterocyclic substituent corresponding to R^2 of the compounds of the present invention.

[0014] According to the present invention, the object compound (I) or a salt thereof can be prepared by processes which are illustrated in the following schemes.

Process 1

[0015]



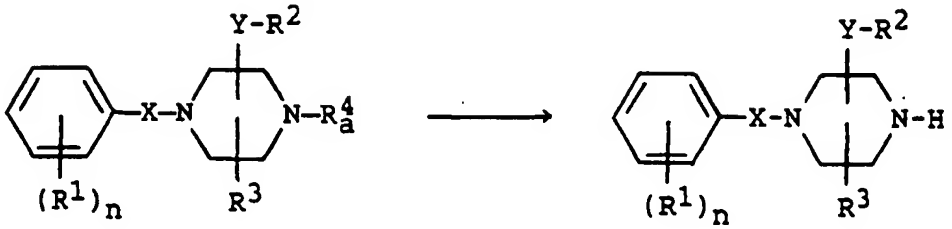
(II) or a salt thereof

(III) or its reactive derivative at the imino group or a salt thereof

(I) or a salt thereof

Process 2

[0016]

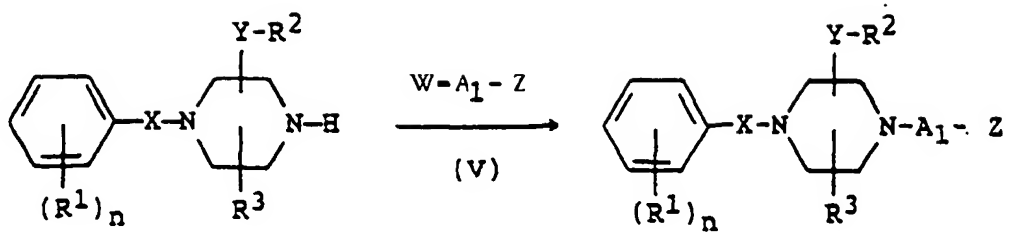


(Iz) or a salt thereof

(Ia) or a salt thereof

Process 3

[0017]

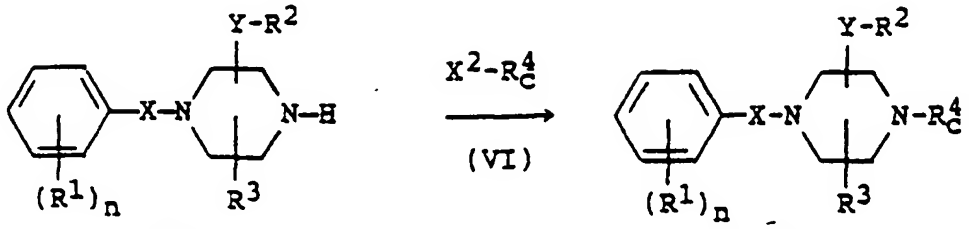


(Ia)
or its reactive derivative at the imino group or a salt thereof

(Ib)
or a salt thereof

Process 4

[0018]

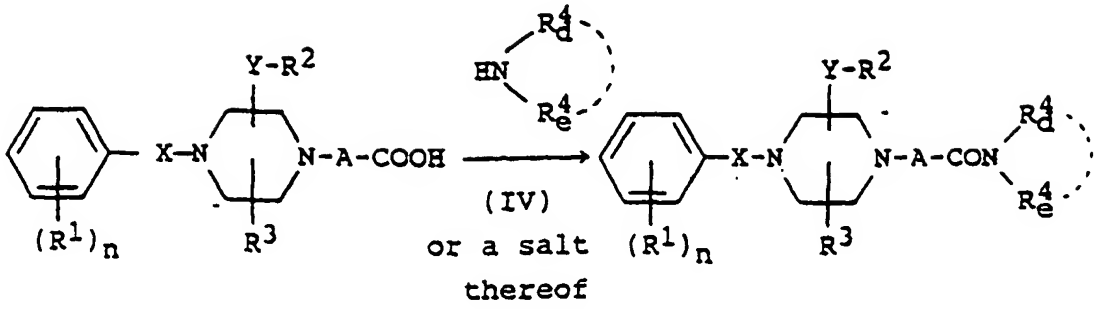


(Ia)
or its reactive derivative at the imino group or a salt thereof

(Ic)
or a salt thereof

Process 5

[0019]

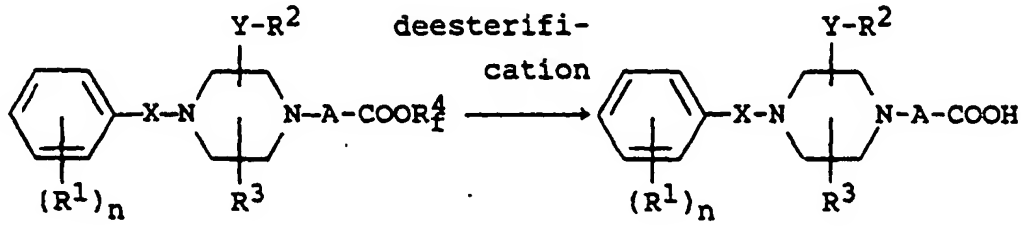


(Id)
or its reactive derivative at the carboxy group or a salt thereof

(Ie)
or a salt thereof

Process 6

[0020]

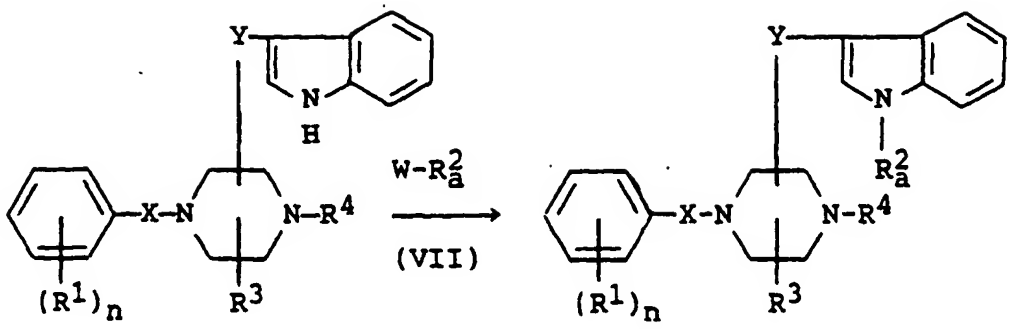


(If)
or a salt thereof

(Ig)
or a salt thereof

Process 7

[0021]



(Ih)
or a salt thereof

(Ii)
or a salt thereof

wherein

X, Y, Z, R^1, R^2, R^3, R^4, n, X^1, X^2, R^2_a, R^4_a, R^4_c, R^4_d, R^4_e, R^4_f, A_1, and W are defined as in claim 5.

[0022] As to the starting compounds (II), (III), (IV), (V), (VI) and (VII), some of them are novel and can be prepared by the procedures described in the Preparations and Examples mentioned later or a conventional manner.

[0023] Throughout the present specification, the amino acids, peptides, protective groups, condensing agents, etc. are expressed by the abbreviations according to the IUPAC-IUB (Commission on Biological Nomenclature) which are in common use in the field of this art.

[0024] Suitable salts and pharmaceutically acceptable salts of the starting and object compounds are conventional non-toxic salt and include an acid addition salt such as an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydroiodide, sulfate, nitrate, phosphate), or a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid), or a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt), an ammonium salt, or an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N' -dibenzylethylenediamine salt).

[0025] In the above and subsequent descriptions of the present specification, suitable examples and illustrations of the various definitions which the present invention include within the scope thereof are explained in detail as follows.

[0026] The term "lower" means 1 to 6, preferably 1 to 4 carbon atom(s), unless otherwise indicated.

[0027] Suitable "lower alkylene" is straight or branched one having 1 to 6 carbon atom(s) and may include methylene, ethylene, trimethylene, propylene, tetramethylene, methylmethylene, methyltrimethylene, and hexamethylene, in which the preferred one is methylene, ethylene, trimethylene or methylmethylene.

[0028] The term "lower alkenylene" means one having one or two double bond(s) in the straight or branched lower alkylene group as defined above.

[0029] Suitable "lower alkenylene" may include one having 2 to 6 carbon atoms such as vinylene, 1-propenylene, 2-propenylene, 1,3-butadienylene, 1-methylvinylene.

[0030] Suitable "lower alkynylene" may include one having 2 to 6 carbon atoms such as ethynylene, propynylene, 2-penten-4-ynylene, etc.

[0031] The term "halogen" is fluoro, chloro, bromo and iodo.

[0032] Suitable "lower alkyl" is straight or branched one having 1 to 6 carbon atom(s) and may include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, and hexyl.

[0033] Suitable "halo(lower)alkyl" may include chloromethyl, bromomethyl, fluoromethyl, iodomethyl, trifluoromethyl, dichloromethyl, 2-fluoroethyl, 1-chloroethyl, and 2-chloroethyl, in which the preferred one is trifluromethyl.

[0034] Suitable "cyclo(lower)alkyl" may include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl.

[0035] Suitable "aryl" may include phenyl, tolyl, xylyl, mesityl, cumenyl, biphenylyl, and naphthyl, in which the preferred one is C_6-C_{10} aryl and the most preferred one is phenyl.

[0036] Suitable "aryloxy" may include phenoxy, tolyloxy, and naphthyloxy.

[0037] Suitable "aromatic hetero(mono- or bi-)cyclic group" may include unsaturated monocyclic or bicyclic heterocyclic group containing at least one hetero atom such as nitrogen and sulfur atoms.

[0038] Preferable "aromatic hetero(mono)cyclic group" may include 5- or 6-membered aromatic hetero(mono)cyclic group containing one to four hetero atoms selected from nitrogen and sulfur atoms and may be exemplified pyrrolyl, pyridyl, thienyl, thiazolyl, isothiazolyl, tetrazolyl, pyrimidinyl, pyrazinyl, pyridazinyl and the like.

[0039] Preferable "aromatic hetero(bi)cyclic group" may include condensed aromatic heterocyclic group containing one, two or three hetero atoms selected from nitrogen and sulfur atoms and may be exemplified benzothienyl, phthalimido, indolyl, indolizinyl, isoindolyl, indazolyl, purinyl, quinolizinyl, isoquinolyl, phthalazinyl, quinazolinyl, cinnolinyl.

[0040] The "aromatic hetero(mono- or bi-)cyclic group" in the definition of R^2 or Z may be bonded to the adjacent "Y" or "A" in the formula (I) at the carbon atom or the hetero atom in the heterocyclic ring.

[0041] The "aromatic hetero(mono- or bi-)cyclic group" in the definition of R^2 may be substituted by a substituent selected from lower alkyl, (di-)lower alkylamino(lower)alkyl (e.g., 2-dimethylaminoethyl).

[0042] More preferable "aromatic hetero(mono- or bi-)cyclic group which may have a substituent" may include 1H-1-(lower alkyl)indol-3-yl.

[0043] Suitable "lower alkoxy" may include methoxy, ethoxy, isopropyloxy, butoxy.

[0044] Suitable "lower alkanesulfonylamino" may include mesylamino, ethanesulfonylamino.

[0045] Suitable "arylsulfonylamino" may include phenylsulfonylamino, naphthylsulfonylamino.

[0046] The "amino" in the definition of R^1 may have 1 or 2 and same or different substituent(s) selected from lower alkyl as defined above, lower alkanesulfonyl (e.g., mesyl, ethanesulfonyl) and acyl as defined below (e.g., lower alkanoyl).

[0047] Preferable "amino which may have 1 or 2 and same or different substituent(s)" may be exemplified by methylamino, dimethylamino, formylamino, acetylamino, N-formyl-N-methylamino, mesylamino.

[0048] Suitable "acyl moiety" may include an aliphatic acyl group, an aromatic acyl group and a saturated heterocyclic carbonyl group and each of which may be substituted by 1 to 3 and same or different suitable substituent (s) as defined below.

[0049] Suitable example of said acyl moiety may include:

(a) aliphatic acyl group

(a-1) optionally substituted carboxy or esterified carboxy group

- Preferable "ester moiety" in the term of "esterified carboxy group" includes the ones such as lower alkyl ester (e.g., methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester), lower alkenyl ester (e.g., vinyl ester, allyl ester), lower alkynyl ester (e.g., ethynyl ester, propynyl ester), and each of which may be substituted by an aryl which may further be substituted by 1 to 3 and same or different substituent(s) selected from the "Substituent list M" as described below.

(a-2) optionally substituted lower alkanoyl group

- Preferable lower alkanoyl group includes formyl, acetyl, propionyl, butyryl, isobutyryl and each of which may have 1 to 3 and same or different substituent(s) selected from the "Substituent list Q" as described below.

(a-3) optionally substituted cyclo(lower)alkylcarbonyl group

- Preferable cyclo(lower)alkylcarbonyl group includes cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, and each of which may have 1 to 3 and same or different substituent(s) selected from the "Substituent list M" as described below.

(a-4) optionally substituted lower alkenoyl group

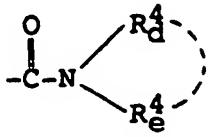
- Preferable lower alkenoyl group includes acryloyl, methacryloyl, crotonoyl, isocrotonoyl, and each of which may have 1 to 3 and same or different substituent(s) selected from the "Substituent list Q" as described below.

(a-5) optionally substituted lower alkynoyl group

- Preferable lower alkynoyl group includes ethynylcarbonyl, propynylcarbonyl, and each of which may have

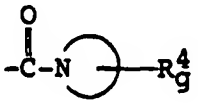
1 to 3 and same or different substituent(s) selected from the "Substituent list Q" as described below.

(a-6) carbamoyl derivative illustrated by the formula :



(wherein R^4_d and R^4_e are defined as in claim 1.)

- Preferable "carbamoyl derivative" includes carbamoyl group, lower alkyl carbamoyl group (e.g., methylcarbamoyl, ethylcarbamoyl), di-(lower alkyl)carbamoyl group (e.g., dimethylcarbamoyl, diethylcarbamoyl), and a group of the formula :



(wherein

is a N containing saturated heterocyclic group and

R^4_g is hydrogen or a group selected from the "Substituent list M" as defined below).

More preferable "N containing saturated heterocyclic group" for

may include 5-, 6- or 7-membered heterocyclic group which contains at least one nitrogen atom as a hetero atom. Most preferable one is 1-pyrrolidinyl, 1-piperidyl, 4-morpholino, 1-piperazinyl, 1-homopiperazinyl, and the heterocyclic group may be substitued by 1 to 3 and same or different substituent(s) selected from the "Substituent list M" as defined below.

(b) aromatic acyl group

(b-1) optionally substituted aroyl group

- Preferable "aroyl group" includes benzoyl, toluoyl, naphthoyl.
  The aroyl group may be substituted by 1 or 2 and same or different substituent(s) as defined in claim 1.

(b-2) optionally substituted aromatic hetero(mono- or bi-)cyclic carbonyl group

- Preferable "aromatic hetero(mono- or bi-)cyclic group moiety" in the "aromatic hetero(mono- or bi-)cyclic carbonyl group" is the one as exemplified before.
  The "aromatic hetero(mono- or bi-)cyclic carbonyl group" may be substituted as defined in claim 1.

(c) optionally substituted saturated heterocyclic carbonyl group

- The "saturated heterocyclic group moiety" in the "saturated heterocyclic carbonyl group" may include 5- or 6-membered heterocyclic group which contains one nitrogen atom as a hetero atom. Most preferable one is pyrrolidinyl, piperidyl.

--- Substituent list M ---

[0050] aryl; aroyl; aryloxy; lower alkyl optionally substituted by hydroxy; ar(lower)alkyl; carbamoyl; cyclo(lower)alkyl; carboxy; cyano; halogen; hydroxy; lower alkanoyl; lower alkanoyloxy; lower alkoxy; amino optionally substituted by 1 or 2 and same or different substituent(s) selected from lower alkyl, aryl, lower alkanoyl, lower alkanesulfonyl and aroyl; oxo; nitro; lower alkoxycarbonyl; N containing saturated heterocyclic group; or aromatic hetero(mono- or bi-)cyclic group.

--- Substituent list Q ---

[0051] aryl optionally substituted by 1 or 2 of amino, halogen, hydroxy, nitro, halo(lower)alkyl, lower alkoxy, lower alkyl, lower alkanoylamino or (mono- or di-)lower alkylamino; aryloxy; aroyl; lower alkoxy; halogen; hydroxy; carbamoyl; lower alkoxycarbonyl which may be substituted by aryl; amino optionally substituted by 1 or 2 and same or different substituent(s) selected from lower alkyl, aryl, lower alkanoyl, lower alkanesulfonyl and aroyl; ureido; N containing saturated heterocyclic group optionally substituted by lower alkyl, aryl or lower alkanoylamino; carboxy; cyclo(lower)alkyl; or aromatic hetero(mono- or bi-)cyclic group optionally substituted by amino, lower alkyl or lower alkanoylamino.

[0052] In the explanation of the above lists of substituent(s), suitable examples and illustrations of the each definitions are the same or equivalent one which are beforementioned, or the one described below :-

- "(mono- or di-)lower alkylamino" may include lower alkylamino and di(lower alkyl)amino.
- suitable "lower alkylamino" may include straight or branched lower alkylamino such as methylamino, ethylamino, isopropylamino, and the lower alkyl moiety may be substituted by 1 to 3 and same or different another substituent (s) selected from the "Substituent list Q", wherein more preferable lower alkylamino is methylamino and benzylamino,
- suitable "di(lower alkyl)amino" may include straight or branched di(lower alkyl)amino such as dimethylamino, diethylamino, methylethylamino, and the lower alkyl moiety may be substituted by 1 to 3 and same or different another substituent(s) selected from the "Substituent list Q", wherein more preferable di(lower alkyl)amino is dimethylamino and N-methyl-N-benzylamino,
- suitable "lower alkoxycarbonyl" may include methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl.

[0053] More preferable compounds of this invention are defined in claims 2 to 4.

[0054] Suitable "leaving group" may include hydroxy, reactive group derived from hydroxy.

[0055] Suitable "reactive group derived from hydroxy" may include acid residue.

[0056] Suitable "acid residue" may include halogen (e.g. fluoro, chloro, bromo, iodo), acyloxy (e.g. acetoxy, tosyloxy, mesyloxy).

[0057] Suitable "imino-protective group" may include ar(lower)alkyl such as benzyl, benzhydryl, phenethyl.

[0058] The Processes 1 to 7 for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

[0059] The object compound (I) or a salt thereof can be prepared by reacting a compound (II) or a salt thereof with a compound (III) or its reactive derivative at the imino group or a salt thereof.

[0060] Suitable reactive derivative at the imino group of the compound (III) may include Schiff's base type imino or its tautomeric enamine type isomer formed by the reaction of the compound (III) with a carbonyl compound such as aldehyde, ketone; a silyl derivative formed by the reaction of the compound (III) with a silyl compound such as bis (trimethylsilyl)acetamide, mono(trimethylsilyl)acetamide, bis(trimethylsilyl)urea; a derivative formed by reaction of the compound (III) with phosphorus trichloride or phosgene.

[0061] Suitable reactive derivative at the carboxy group and the sulfo group of the compound (II) may include an acid halide, an acid anhydride, an activated amide, an activated ester, a lower alkyl ester.

Suitable examples of the reactive derivatives may be an acid chloride;
an acid azide; a mixed acid anhydride with an acid such as substituted phosphoric acid [e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid], dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, sulfuric acid, sulfonic acid [e.g. methanesulfonic acid], aliphatic carboxylic

acid [e.g. acetic acid, propionic acid, butyric acid, isobutyric acid, pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid, trichloroacetic acid] or aromatic carboxylic acid [e.g. benzoic acid]; a symmetrical acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester [e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl

ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester], or an ester with a N-hydroxy compound [e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxyphthalimide, 1-hydroxy-1H-benzotriazole]. These reactive derivatives can optionally be selected from the above according to the kind of the compound (II) to be used.

[0062] The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol], acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvent which does not adversely influence the reaction. These conventional solvent may also be used in a mixture with water.

[0063] In this reaction, when the compound (II) is used in a free acid form or its salt form, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; pentamethyleneketene-N-cyclohexylimine; diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; diphenyl phosphorylazide; thionyl chloride; oxalyl chloride; lower alkyl haloformate [e.g. ethyl chloroformate, isopropyl chloroformate]; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxaozlium hydroxide intramolecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; 2-chloro-1-methylpyridinium iodide; 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, trichloromethyl chloroformate, phosphorus oxychloride.

[0064] The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorpholine, N,N-di(lower)alkylbenzylamine.

[0065] The reaction temperature is not critical, and the reaction is usually carried out under cooling to warming.

Process 2

[0066] The object compound (Ia) or a salt thereof can be prepared by subjecting the compound (Iz) or a salt thereof to elimination reaction of the imino-protective group.

[0067] In the present elimination reaction, all conventional methods used in the elimination reaction of the imino-protective group, for example, hydrolysis, reduction, elimination using base or acid are applicable.

[0068] Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide), alkali metal carbonate (e.g. sodium carbonate, potassium carbonate), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate), alkali metal acetate (e.g. sodium acetate, potassium acetate), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate), and an organic base such as trialkylamine (e.g. trimethylamine, triethylamine), picoline, N-methylpyrrolidine, N-methylmorpholine,
1,5-diazabicyclo[4.3.0]non-5-one,
1,4-diazabicyclo[2.2.2]octane,
1,5-diazabicyclo[5.4.0]undecene-5. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

[0069] Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid).

[0070] The present hydrolysis is usually carried out in an organic solvent, water or a mixed solvent thereof.

[0071] The reaction temperature is not critical, and it may suitably be selected in accordance with the kind of the imino-protective group and the elimination method.

[0072] The elimination using Lewis acid is preferable to eliminate substituted or unsubstituted ar(lower)alkyl ester and carried out by reacting the compound (Iz) or a salt thereof with Lewis acid such as boron trihalide (e.g. boron

trichloride, boron trifluoride), titanium tetrahalide (e.g. titanium tetrachloride, titanium tetrabromide), tin tetrahalide (e.g. tin tetrachloride, tin tetrabromide), aluminum halide (e.g. aluminum chloride, aluminum bromide), trihaloacetic acid (e.g. trichloroacetic acid, trifluoroacetic acid). This elimination reaction is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol) and is usually carried out in a solvent such as nitroalkane (e.g. nitromethane, nitroethane), alkylene halide (e.g. methylene chloride, ethylene chloride), diethyl ether, carbon disulfide or any other solvent which does not adversely affect the reaction. These solvents may be used as a mixture thereof.

[0073] The reduction elimination can be applied preferably for elimination of the protective group such as halo(lower) alkyl (e.g. 2-iodoethyl, 2,2,2-trichloroethyl) ester, ar(lower)alkyl (e.g. benzyl) ester.

[0074] The reduction method applicable for the elimination reaction may include, for example, reduction by using a combination of a metal (e.g. zinc, zinc amalgam) or a salt of chromium compound (e.g. chromous chloride, chromous acetate) and an organic or an inorganic acid (e.g. acetic acid, propionic acid, hydrochloric acid); and conventional catalytic reduction in the presence of a conventional metallic catalyst (e.g. palladium carbon, Raney nickel).

[0075] The reaction temperature is not critical, and the reaction is usually carried out under cooling, at ambient temperature or under warming.

Process 3

[0076] The object compound (Ib) or a salt thereof can be prepared by reacting the compound (Ia) or its reactive derivative at the imino group or a salt thereof with the compound (V) or a salt thereof.

[0077] Suitable example of the reactive derivative at the imino group of the compound (Ia) is the one as exemplified for compound (III) in the Process 1.

[0078] This reaction is usually carried out in a solvent such as alcohol [e.g. methanol, ethanol], dichloromethane, benzene, N,N-dimethylformamide, tetrahydrofuran, diethyl ether or any other solvent which does not adversely affect the reaction.

[0079] The reaction may be carried out in the presence of an inorganic or an organic base such as an alkali metal hydroxide [e.g. sodium hydroxide, potassium hydroxide], an alkali metal carbonate [e.g. sodium carbonate, potassium carbonate], an alkali metal bicarbonate [e.g. sodium bicarbonate, potassium bicarbonate], alkali metal hydride [e.g. sodium hydride, potassium hydride], tri(lower)alkylamine [e.g. trimethylamine, triethylamine, diisopropylethylamine], pyridine or its derivative [e.g. picoline, lutidine, 4-dimethylaminopyridine]. In case that the base to be used is liquid, it can also be used as a solvent.

[0080] The reaction temperature is not critical, and the reaction can be carried out under cooling, at room temperature or under warming or heating.

Process 4

[0081] The object compound (Ic) or a salt thereof can be prepared by reacting the compound (Ia) or its reactive derivative at the imino group or a salt thereof with the compound (VI) or a salt thereof.

[0082] Suitable example of the reactive derivative at the imino group of the compound (Ia) is the one as exemplified in the Process 1.

[0083] This reaction can be carried out in substantially the same manner as the Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature] of this reaction are to be referred to those as explained in the Process 1.

Process 5

[0084] The compound (Ie) or a salt thereof can be prepared by reacting a compound (Id) or its reactive derivative at the carboxy group or a salt thereof with a compound (IV) or a salt thereof.

[0085] Suitable example of the reactive derivative at the carboxy group of the compound (Id) is the one as exemplified for compound (II) in the Process 1.

[0086] This reaction can be carried out in substantially the same manner as the Process 1, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature] of this reaction are to be referred to those as explained in the Process 1.

Process 6

[0087] The compound (Ig) or a salt thereof can be prepared by subjecting a compound (If) or a salt thereof to deesterification reaction.

[0088] The reaction is carried out in accordance with a conventional method such as hydrolysis or reduction.

[0089] The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid. Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium], an alkaline earth metal [e.g. magnesium, calcium], the hydroxide or carbonate or bicarbonate thereof, trialkylamine [e.g. trimethylamine, triethylamine], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo [5.4.0]undec-7-ene. Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid], an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, hydriodic acid, sulfuric acid] and Lewis acid [e.g. boron tribromide].

[0090] The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical, and the reaction can be usually carried out under cooling, at ambient temperature or under warming.

[0091] The reduction can be applied preferably for elimination of the ester moiety such as 4-nitrobenzyl, 2-iodoethyl, 2,2,2-trichloroethyl. The reduction method applicable for the elimination reaction may include chemical reduction and catalytic reduction.

[0092] Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron] or metallic compound [e.g. chromium chloride, chromium acetate] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid].

[0093] Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire], palladium catalyst [e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel], cobalt catalyst [e.g. reduced cobalt, Raney cobalt], iron catalyst [e.g. reduced iron, Raney iron], copper catalyst [e.g. reduced copper, Raney copper, Ullman copper].

[0094] The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, an alcohol [e.g. methanol, ethanol, propanol], N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. Further, a suitable solvent to be used in catalytic reduction may be the above-mentioned solvent, and other conventional solvent such as diethyl ether, dioxane, tetrahydrofuran, or a mixture thereof.

[0095] The reaction temperature of this reduction is not critical, and the reaction can be usually carried out under cooling, at ambient temperature or under warming.

Process 7

[0096] The object compound (Ii) or a salt thereof can be prepared by reacting the compound (Ih) or a salt thereof with the compound (VII) or a salt thereof.

[0097] This reaction can be carried out in substantially the same manner as the Process 3, and therefore the reaction mode and reaction conditions [e.g. solvents, reaction temperature] of this reaction are to be referred to those as explained in the Process 3.

[0098] It is to be noted that the compound (I) and the other compounds may include one or more stereoisomers due to asymmetric carbon atoms, and all of such isomers and mixture thereof are included within the scope of this invention.

[0099] The object compound (I) and a pharmaceutically acceptable salt thereof have pharmacological activities such as Tachykinin antagonism, especially Substance P antagonism, Neurokinin A antagonism or Neurokinin B antagonism, and therefore are useful for treating or preventing Tachykinin-mediated diseases, particularly Substance P-mediated diseases, for example, respiratory diseases such as asthma, bronchitis (e.g. chronic bronchitis, acute bronchitis and diffuse panbronchiolitis), rhinitis, cough, expectoration; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; inflammatory diseases such as rheumatoid arthritis, osteoarthritis;
pains or aches (e.g. migraine, headache, cluster headache, toothache, cancerous pain, back pain, neuralgia).

[0100] Further, it is expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing ophthalmic diseases such as glaucoma, uveitis; gastrointestinal diseases such as ulcer, ulcerative colitis, irritable bowel syndrome, food allergy; inflammatory diseases such as nephritis; circulatory diseases such as hypertension, angina pectoris, cardiac failure, thrombosis, Raynaud's disease; epilepsy; spastic paralysis; pollakiuria; cystitis; bladder detrusor hyperreflexia; urinary incontinence; dementia; AIDS related dementia; Alzheimer's diseases; Down's syndrome; Huntington's chorea; carcinoid syndrome; disorders related to immune enhancement or suppression.

[0101] It is furthermore expected that the object compound (I) and a pharmaceutically acceptable salt thereof of the present invention are useful for treating or preventing chronic obstructive pulmonary diseases, particularly chronic pulmonary emphysema; iritis; proliferative vitreoretinopathy; psoriasis; inflammatory intestinal diseases, particularly

Crohn's diseases; hepatitis; superficial pain on congelation, burn, herpes zoster or diabetic neuropathy; tenalgia attended to hyperlipidemia; postoperative neuroma, particularly of mastectomy; vulvar vestibulitis; hemodialysis-associated itching; lichen planus; laryngopharyngitis; bronchiectasis; coniosis; whooping cough; pulmonary tuberculosis; cystic fibrosis; emesis; mental diseases, particularly anxiety, depression, dysthymic disorders and schizophrenia; demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis; attenuation of morphine withdrawal; oedema, such as oedema caused by thermal injury; small cell carcinomas, particularly small cell lung cancer (SCLC); hypersensitivity disorders such as poison ivy; fibrosing and collagen diseases such as scleroderma and eosinophilic fasciloliasis; reflex sympathetic dystrophy such as shoulder/hand syndrome; addiction disorders such as alcoholism; stress related somatic disorders; rheumatic diseases such as fibrositis.

[0102] For therapeutic purpose, the compound (I) and a pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compound, as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral, external including topical, enteral, intravenous, intramuscular, inhalant, nasal, intraarticular, intraspinal, transtracheal or transocular administration. The pharmaceutical preparations may be solid, semi-solid or solutions such as capsules, tablets, pellets, dragees, powders, granules, suppositories, ointments, creams, lotions, Inhalants, injections, cataplasms, gels, tapes, eye drops, solution, syrups, aerosols, suspension, emulsion. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

[0103] While the dosage of the compound (I) will vary depending upon the age and condition of a patient, an average single dose of about 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the compound (I) may be effective for treating Tachykinin-mediated diseases such as asthma. In general, amounts between 0.1 mg/body and about 1,000 mg/body may be administered per day.

[0104] In order to illustrate the usefulness of the object compound (I) and a pharmaceutically acceptable salt thereof, the pharmacological test data of some representative compounds of the present invention are shown in the following.

[0105] All of the following Test Compounds showed more than 90% inhibition rate of ^{3}H-Substance P binding to guinea pig lung membranes at the concentration of 1 μg/ml.

Test Compounds : The object compounds of the Examples 17-1, 19-1, and 24-4.

^{3}H-Substance P Binding to Guinea Pig Lung Membranes

Test Method : ^{3}H-Substance P Binding to Guinea Pig Lung Membranes

[0106]

(a) Crude lung membrane preparation

Male Hartly strain guinea pigs were stunned and bled. The trachea and lung were removed and homogenized in ice-cold buffer (0.25 M sucrose, 50 mM Tris-HCl pH 7.5, 0.1 mM EDTA) by using Polytoron (Kinematica). The homogenate was centrifuged (1000 x g, 10 minutes) to remove tissue clumps and the supernatant was centrifuged (35000 x g, 20 minutes) to yield pellet. The pellet was resuspended in buffer (5 mM Tris-HCl pH 7.5), homogenized with a teflon homogenizer and centrifuged (35000 x g, 20 minutes) to yield pellet which was referred to as crude membrane fractions. The obtained pellet was resuspended in buffer (50 mM Tris-HCl pH 7.5) and stored at -70°C until use.

(b) ^{3}H-Substance P binding to preparation membrane

Frozen crude membrane fractions were thawed and resuspended in Medium 1 (50 mM Tris-HCl pH 7.5, 1 mM $MnCl_2$, 0.02% BSA, 2 μg/ml chymostatin, 4 μg/ml leupeptin, 40 μg/ml bacitracin, 10 μM phosphoramidon). ^{3}H-Substance P (1 nM) was incubated with 100 μl of the membrane preparations with or without test compounds in Medium 1 at 25°C for 30 minutes in a final volume of 500 μl. At the end of the incubation period, 5 ml ice-cold 50 mM Tris-HCl buffer was added to each tube and its content was quickly filtered over a Whatman GF/B glass filter (pretreated with 0.1% polyethylene imine for 3 hours prior to use) under aspiration. Each of the filters was then washed four times with 5 ml of ice-cold buffer (50 mM Tris-HCl pH 7.5). The radioactivity was counted in 5 ml of Aquazol-2 in Packard scintillation counter (Packard TRI-CARB 4530). All data presented and specific binding defined as that displaceable by 5 μM unlabeled Substance P.

[0107] All of the following Test Compounds showed more than 90% inhibition rate of ^{125}I-BH-Substance P binding to h-NK_1 receptors at the concentration of 0.1 μg/ml.

Test Compounds : The object compounds of the Examples 17-50, 17-56, 17-57, 19-13, 25-2 and 26

^{125}I-BH-Substance P Binding to h-NK$_1$ Receptors

Test Method : ^{125}I-BH-Substance P Binding to h-NK$_1$ Receptors

[0108]

(a) Crude CHO cell membrane preparation

CHO cells permanently expressing h-NK$_1$ receptors were harvested and homogenized with a Dounce homogenizer at 4°C in a buffer (0.25 M sucrose, 25 mM Tris-HCl pH 7.4, 10 mM $MgCl_2$, 1 mM EDTA, 5 µg/ml p-APMSF). The homogenate was centrifuged (500 x g, 10 minutes), and the pellet was resuspended in the same buffer, homogenized, and centrifuged. The two supernatants were combined and centrifuged (100,000 x g, 1 hour). The crude cell membranes thus isolated were resuspended in buffer (25 mM Tris-HCl pH 7.4, 10 mM $MgCl_2$, 1 mM EDTA, 5 µg/ml p-APMSF) and stored at -80°C until use.

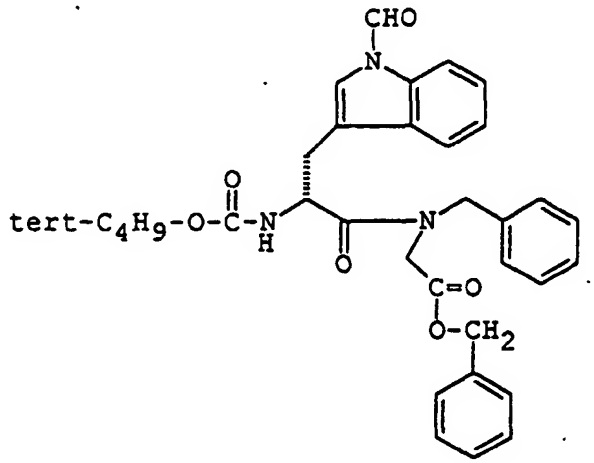
(b) ^{125}I-BH-Substance P binding to preparation membrane

Cell membranes (6 µg/ml) were incubated with ^{125}I-BH-Substance P (0.1 nM) with or without test compounds in 0.25 ml of Medium 2(50 mM Trls-HCl pH 7.4, 5 mM $MnCl_2$, 20 µg/ml chymostatin, 40 µg/ml bacitracin, 4 µg/ml leupeptin, 5 µg/ml p-APMSF, 200 µg/ml BSA) at 22°C for 90 minutes. At the end of the incubation period, the content was quickly filtered over a Whatman GF/C glass filter (pretreated with 0.1% polyethylene imine for 3 hours prior to use) under aspiration. Each of the filters was then washed four times with 5 ml of buffer (50 mM Tris-HCl pH 7.4, 5 mM $MnCl_2$). The radioactivity was counted by using Auto Gamma counter (Packard RIASTAR 5420A). All data presented are specific binding defined as that displaceable by 3 µM unlabeled Substance P.

[0109] The following Preparations and Examples are given for the purpose of illustrating this invention.

Preparation 1

[0110]



[0111] To a mixture of N^2-(tert-butoxycarbonyl)-N^1-formyl-D-tryptophan (3.99 g) and N-benzyl glycin benzyl ester hydrochloride (3.50 g) in dichloromethane (70 ml) was added triethylamine (5.85 ml) under nitrogen atmosphere. To the mixture was added 2-chloro-1-methylpyridinium iodide (3.67 g) at room temperature, and the resulting mixture was stirred for 2 hours. After the reaction was completed, dichloromethane (30 ml) and water (30 ml) were added. The organic layer was separated, washed with 0.5N hydrochloric acid (10 ml), water (10 ml), aqueous sodium bicarbonate solution (10 ml) and brine (20 ml) successively and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified on a silica gel column (140 g) eluting with a mixture of toluene and ethyl acetate (4:1) to give (2R)-N-benzyl-N-benzyloxycarbonylmethyl-2-(tert-butoxycarbonylamino)-3-(N-formyl-1H-indol-3-yl)propanamide (6.41 g) as an oil.

IR ($CHCl_3$) : 3300, 2970, 1740, 1700, 1644, 1604 cm^{-1}
NMR (DMSO-d_6, δ) : 0.89, 1.22 and 1.29 (9H, 3 s); 2.80-3.10 (2H, m); 3.95-4.25 (2H, m); 4.40-4.90 (3H, m); 4.95-5.20 (2H, m); 7.05-7.75 (15H, m); 7.98 and 8.22 (1H, 2 br s); 9.22 and 9.61 (1H, 2 br s)
MASS : 570 (M+1)

Preparation 2

[0112] The following compounds were obtained according to a similar manner to that of Preparation 1.

1) (2R)-N-Benzyl-N-benzyloxycarbonylmethyl-2-(tert-butoxycarbonylamino)-3-(3,4-dimethylphenyl)propanamide

IR (Neat) : 3300, 1740, 1700, 1645, 1500, 1360 cm^{-1}
NMR ($CDCl_3$, δ) :1.40 (9H, s); 2.2-2.3 (6H, m); 2.8-3.2 (2H, m); 3.7-4.2 (2H, m); 4.5-5.0 (3H, m); 5.1-5.2 (2H, m); 5.2-5.3 (1H, m); 6.9-7.1 (5H, m); 7.2-7.5 (8H, m)
MASS : 531 (M+1), 475, 431

2) (2S)-N-Benzyl-N-benzyloxycarbonylmethyl-2-(tert-butoxycarbonylamino)-3-(N-formyl-1H-indol-3-yl)propanamide

IR (Neat) : 3300, 1700, 1650, 1460 cm^{-1}
MASS : 570 (M+1), 514, 470

3) (2R)-N-Benzyl-N-benzyloxycarbonylmethyl-2-(tert-butoxycarbonylamino)-3-phenylpropanamide

IR (Neat) : 3300, 1750-1630, 1150, 1013, 725 cm^{-1}
NMR ($CDCl_3$, δ) : 1.38 and 1.62 (9H, 2 br s); 2.87-3.16 (2H, m); 3.74-4.73 (5H, m); 4.94-5.28 (3H, m); 7.02-7.37 (15H, m)

4) (2R)-N-Benzyl-N-benzyloxycarbonylmethyl-2-(tert-butoxycarbonylamino)-3-(3,4-dichlorophenyl)propanamide

mp : 171-172°C
IR (Nujol) : 3250, 1730, 1680, 1645, 1520, 1360 cm^{-1}
NMR (DMSO-d_6, δ) : 1.2-1.4 (9H, m); 2.7-3.0 (2H, m); 3.9-4.3 (2H, m); 4.4-4.8 (3H, m); 5.12 (2H, s); 7.0-7.5 (14H, m)
MASS : 571 (M+1), 515, 471, 363

5) (2R) -N-Benzyl-N-benzyloxycarbonylmethyl-2- (tert-butoxycarbonylamino)-3-(benzo[b]thiophen-3-yl)propanamide

IR (Neat) : 3400, 3300, 1725, 1700, 1640, 1490, 1440, 1380, 1360 cm^{-1}
NMR ($CDCl_3$, δ) : 1.1-1.4 (9H, m); 3.2-3.5 (2H, m); 3.6-4.8 (4H, m); 4.8-5.4 (4H, m); 6.8-7.1 (2H, m); 7.1-7.4 (11H, m); 7.7-8.0 (2H, m)
MASS : 559 (M+1), 503, 459, 351

6) (2S)-N-Benzyl-N-benzyloxycarbonylmethyl-2-(tert-butoxycarbonylamino)-3-(3,4-dimethylphenyl)propanamide

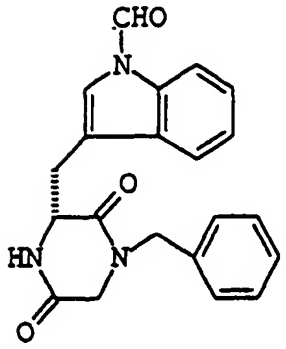
IR (Neat) : 3300, 2960, 2920, 1742, 1700, 1646 cm^{-1}
NMR ($CDCl_3$, δ) : 1.40 (9H, s); 2.18, 2.21 and 2.22 (6H, 3 s); 2.78-3.14 (2H, m); 3.73-4.15 (2H, m); 4.44-5.35 (5H, m); 6.85-7.40 (14H, m)
MASS : 531 (M+1)

7) (2R,3R)-N-Benzyl-N-benzyloxycarbonylmethyl-2-(tert-butoxycarbonylamino)-3-(N-methyl-1H-indol-3-yl)butanamide

IR (Neat) : 3400, 3300, 1740, 1700, 1640, 1480, 1450, 1360 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-1.5 (9H, m); 3.6-5.4 (15H, m); 7.0-7.8 (15H, m)
MASS : 570 (M+1), 538, 514, 471

Preparation 3

[0113]



[0114] To an ice-cooled solution of the object compound of Preparation 1 (6.39 g) in dichloromethane (50 ml) was added 4N hydrogen chloride in dioxane solution (50 ml). The mixture was stirred at the same temperature for 30 minutes and at room temperature for 1 hour. After evaporation of the solvent, the residue was partitioned between dichloromethane (50 ml) and aqueous sodium bicarbonate solution (30 ml). The organic layer was separated, dried over magnesium sulfate and filtered. To the filtrate was added triethylamine (1.67 ml) at room temperature, and the mixture was stirred for 1.5 hours. After evaporation, the residue was triturated with diisopropyl ether, collected by filtration and dried to give (3R)-1-benzyl-3-(N-formyl-1H-indol-3-ylmethyl)piperazine-2,5-dione (3.93 g).

mp : 176-178°C
IR (Nujol) : 3250, 1709, 1648, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 2.95-3.30 and 3.35-3.70 (4H, 2 m); 4.22 (1H, d, J=14.6Hz); 4.30-4.40 (1H, m); 4.54 (1H, d, J=14.9Hz); 6.80-7.75 (9H, m); 7.95-8.50 (2H, m); 9.20 and 9.65 (1H, 2 br s)
MASS : 362 (M+1)

Preparation 4

[0115] The following compounds were obtained according to a similar manner to that of Preparation 3.

1) (3R)-1-Benzyl-3-(3,4-dimethylbenzyl)piperazine-2,5-dione

mp : 191-192°C
$[\alpha]_D^{25}$: -23.3° (C=1, DMF)
IR (Nujol) : 3180, 1640, 1500, 1340 cm^{-1}
NMR (DMSO-d_6, δ) : 2.11 and 2.16 (3H, 2 s); 2.82(1H, dd, J=4.8 and 13.5Hz); 3.13 (1H, dd, J=4.2 and 13.5Hz); 2.76 (1H, d, J=17.1Hz); 3.46 (1H, d, J=17.1Hz); 4.22 (1H, d, J=14.5Hz); 4.55 (1H, d, J=14.5Hz); 4.2-4.3 (1H, m); 6.7-6.9 (3H, m); 7.0-7.1 (2H, m); 7.2-7.3 (3H, m); 8.31 (1H, s)
MASS : 323 (M+1)

2) (3S)-1-Benzyl-3-(N-formyl-1H-indol-3-yl-methyl)piperazine-2,5-dione

mp : 183-184°C
IR (Nujol) : 3250, 1710, 1650 cm^{-1}
NMR (DMSO-d_6, δ) : 3.0-4.6 (7H, m); 6.9-8.5 (10H, m); 8.4 (1H, s); 9.2 (1H, s); 10.9 (1H, s)
MASS : 362 (M+1)

3) (3R)-1-Benzyl-3-benzylpiperazine-2,5-dione

mp : 180-181°C
IR (Nujol) : 3240, 1675-1630, 1315, 1205, 1183, 1101, 1058, 740, 700 cm^{-1}

NMR ($CDCl_3$, δ) : 2.92-3.56 (4H, m); 4.34-4.40 (1H, m); 4.48 (2H, s); 6.66 (1H, s); 7.13-7.36 (10H, m)

4) (3R)-1-Benzyl-3-(3,4-dichlorobenzyl)piperazine-2,5-dione

mp : 167-168°C
$[\alpha]_D^{25}$: -12.8° (C=1.0, DMF)
IR (Nujol) : 3250, 1670, 1645, 1440, 1320 cm^{-1}
NMR (DMSO-d_6, δ) : 2.94 (1H, dd, J=4.8 and 13.4Hz); 3.18 (1H, dd, J=4.8 and 13.4Hz); 3.19 (1H, d, J=17.4Hz); 3.67 (1H, d, J=17.4Hz); 4.19 (1H, d, J=14.6Hz); 4.3-4.4 (1H, m); 4.72 (1H, d, J=14.6Hz); 7.0-7.2 (3H, m); 7.3-7.4 (3H, m); 7.4-7.5 (2H, m); 8.35-8.45 (1H, m)
MASS : 363 (M+1)

5) (3R)-1-Benzyl-3-(benzo[b]thiophen-3-yl-methyl)piperazine-2,5-dione

mp : 213-215°C
$[\alpha]_D^{25}$: +73.5° (C=1.0, DMF)
IR (Nujol) : 3250, 1675, 1645, 1430, 1340, 1315 cm^{-1}
NMR (DMSO-d_6, δ) : 2.94 (1H, d, J=17.3Hz); 3.21 (1H, dd, J=4.5 and 14.5Hz); 3.43 (1H, dd, J=4.5 and 14.5Hz); 3.46 (1H, d, J=17.3Hz); 4.23 (1H, d, J=14.5Hz); 4.38 (1H, d, J=14.5Hz); 4.3-4.4 (1H, m); 6.9-7.1 (2H, m); 7.2-7.5 (6H, m); 7.8-8.1 (2H, m); 8.41 (1H, s)
MASS : 351 (M+1)

6) (3S)-1-Benzyl-3-(3,4-dimethylbenzyl)piperazine-2,5-dione

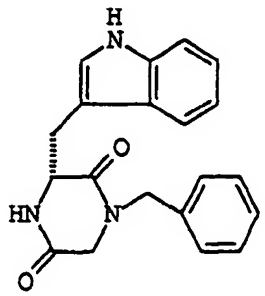
mp : 188-189°C
$[\alpha]_D^{25}$: +22.7° (C=1.0, DMF)
IR (Nujol) : 3200, 1653 cm^{-1}
NMR (DMSO-d_6, δ) : 2.11 (3H, s); 2.16 (3H, s); 2.77 (1H, d, J=17.0Hz); 2.83 (1H, dd, J=13.5, 4.8Hz); 3.07 (1H, dd, J=13.5, 4.2Hz); 3.45 (1H, d, J=17.2Hz); 4.22 (1H, m); 4.23 (1H, d, J=14.4Hz); 4.55 (1H, d, J=14.6Hz); 6.74-6.95 (3H, m); 7.04-7.38 (5H, m); 8.30 (1H, s)
MASS : 323 (M+1)

7) (3R)-1-Benzyl-3-[(1R)-1-(N-methyl-1H-indol-3-yl)ethyl]piperazine-2,5-dione

mp : >240°C
$[\alpha]_D^{25}$: +4.6° (C=1.0, DMF)
IR (Nujol) : 3250, 1670, 1650, 1330, 1310 cm^{-1}
NMR (DMSO-d_6, δ) : 1.39 (3H, d, J=7.4Hz); 2.22 (1H, d, J=17.2Hz); 3.09 (1H, d, J=17.2Hz); 3.67 (3H, s); 3.7-3.8 (1H, m); 3.78 (1H, d, J=14.8Hz); 4.0-4.1 (1H, m); 4.28 (1H, d, J=14.8Hz); 6.7-6.9 (2H, m); 7.0-7.2 (6H, m); 7.40 (1H, d, J=8.1Hz); 7.52 (1H, d, J=7.9Hz); 8.60 (1H, d, J=1.0Hz)
MASS : 362 (M+1), 339

Preparation 5

[0116]



[0117] To an ice-cooled solution of the object compound of Preparation 3 (3.89 g) in a mixture of methanol (175 ml) and tetrahydrofuran (50 ml) was added aqueous 0.1N sodium hydroxide solution (108 ml). The mixture was stirred at the same temperature for 30 minutes and at room temperature for 1.5 hours. After evaporation of the solvent, the residue was extracted with dichloromethane. The organic layer was washed with water and an aqueous sodium chloride solution, and dried over magnesium sulfate. Evaporation of the solvent gave (3R)-1-benzyl-3-(1H-indol-3-yl-methyl) piperazine-2,5-dione (3.68 g).

mp : 207-208°C
IR (Nujol) : 3402, 1650 cm^{-1}
NMR (DMSO-d_6, δ) : 2.68 (1H, d, J=17.2Hz); 3.04 (1H, dd, J=14.4 and 4.4Hz); 3.20-3.40 (2H, m); 4.24 (1H, s); 4.10-4.40 (2H, m); 6.75-7.60 (10H, m); 8.35 (1H, s); 10.94 (1H, s)
MASS : 334 (M+1)

Preparation 6

[0118] The following compounds were obtained according to a similar manner to that of Preparation 5.

1) (3S)-1-Benzyl-3-(1H-indol-3-yl-methyl)piperazine-2,5-dione

mp : 210-211°C
$[\alpha]_D^{25}$: +48.1° (C=1.0, DMF)
IR (Nujol) : 3400, 3225, 1650, 1455 cm^{-1}
NMR (DMSO-d_6, δ) : 3.0-3.4 (3H, m); 4.2 (4H, s); 6.8-7.6 (10H, m); 8.4 (1H, s)
MASS : 334 (M+1)

2) (3R,6R)-1-Benzyl-3-(1H-indol-3-yl-methyl)-6-methylpiperazine-2,5-dione

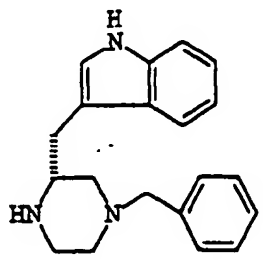
$[\alpha]_D^{19}$: +5.9° (C=1.0, MeOH)
IR (Neat) : 3250, 1675, 1635, 1450, 1320 cm^{-1}
NMR (DMSO-d_6, δ) : 0.35 (3H, d, J=7Hz); 3.00-4.86 (6H, m); 6.95-8.32 (11H, m); 10.94 (1H, s)
MASS : 348 (M+1)

3) (3R,6S)-1-Benzyl-3-(1H-indol-3-yl-methyl)-6-methylpiperazine-2,5-dione

IR (Neat) : 3260, 1670, 1450, 1320 cm^{-1}
MASS : 348 (M+1)

Preparation 7

[0119]



[0120] To a suspension of lithium aluminum hydride (0.77 g) in tetrahydrofuran (40 ml) was added dropwise a solution of the object compound of Preparation 5 (3.40 g) in tetrahydrofuran (40 ml) at 0°C under nitrogen atmosphere. The mixture was stirred at room temperature for 50 minutes and at refluxing temperature for 1 hour. The resulting mixture was diluted with tetrahydrofuran (60 ml) and cooled to 0°C. Water (3.0 ml) and aqueous 15% sodium hydroxide solution (0.8 ml) were added slowly. The resulting insoluble inorganic material was removed by filtration and washed with tetrahydrofuran. The filtrate and the washing were combined and evaporated under reduced pressure to give (3R)-

1-benzyl-3-(1H-indol-3-yl-methyl)piperazine (3.68 g) as an oil.

IR ($CHCl_3$) : 3240, 3040, 2900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.70-2.00 and 2.30-2.45 (2H, 2 m); 2.50-3.00 (7H, m); 3.25-3.60 (3H, m); 6.80-7.60 (10H, m); 10.80 (1H, s)
MASS : 306 (M+1)

Preparation 8

[0121] The following compounds were obtained according to a similar manner to that of Preparation 7.

1) (3R)-1-Benzyl-3-(3,4-dimethylbenzyl)piperazine

IR (Neat) : 3000-2750, 1670, 1500, 1450, 1360, 1320 cm^{-1}
NMR ($CDCl_3$, δ) : 2.26 (6H, m); 1.8-3.0 (9H, m); 3.4-3.6 (2H, m); 6.9-7.1 (3H, m); 7.2-7.5 (5H, m)
MASS : 295 (M+1)

2) (3R)-1,3-Dibenzylpiperazine

IR (Neat) : 3020, 2850, 2800, 1600, 1493, 1453, 1322, 1134, 1027, 735, 697 cm^{-1}
NMR ($CDCl_3$, δ) : 1.68-2.15 (4H, m); 2.48-3.00 (6H, m), 3.43-3.58 (2H, m); 7.18-7.33 (10H, m)

3) (3S)-1-Benzyl-3-(1H-indol-3-yl-methyl)piperazine $[\alpha]_D^{25}$: +13.0° (C=1.0, DMF)

IR (Neat) : 3400, 3150, 3025, 1450 cm^{-1}
NMR (DMSO-d_6, δ) : 1.7-3.4 (9H, m); 6.9-7.5 (10H, m); 10.8 (1H, s)
MASS : 306 (M+1)

4) (3R)-1-Benzyl-3-(3,4-dichlorobenzyl)piperazine

IR (Neat) : 3200 (br), 3100-2700, 1660, 1590, 1550, 1490, 1460, 1450, 1400, 1320 cm^{-1}
NMR ($CDCl_3$, δ) : 1.8-2.2 (3H, m); 2.4-3.0 (7H, m); 3.4-3.6 (2H, m); 7.02 (1H, dd, J=2.0 and 8.2Hz); 7.2-7.4 (7H, m)
MASS : 335 (M+1)

5) (3R)-1-Benzyl-3-(benzo[b]thiophen-3-yl-methyl)piperazine

IR (Neat) : 2600-3100, 1660, 1490, 1450, 1425 cm^{-1}
NMR ($CDCl_3$, δ) : 1.8-2.2 (4H, m); 2.7-3.3 (6H, m); 3.4-3.6 (2H, m); 7.1-7.5 (8H, m); 7.7-8.0 (2H, m)
MASS : 323 (M+1)

6) (3S)-1-Benzyl-3-(3,4-dimethylbenzyl)piperazine

IR (Neat) : 3310-3250, 3020, 2930, 2800, 1668 cm^{-1}
NMR ($CDCl_3$, δ) : 1.70 (1H, br s); 1.80-3.60 (11H, m); 2.23 (6H, s); 6.83-7.40 (8H, m)
MASS : 295 (M+1)

7) (3R)-1-Benzyl-3-[(1R)-1-(N-methyl-1H-indol-3-yl)ethyl]piperazine

8) (3R,6R)-1-Benzyl-3-(1H-indol-3-yl-methyl)-6-methylpiperazine

$[\alpha]_D^{19}$: -21.2° (C=1.0, MeOH)
IR (Neat) : 3400, 3200, 1650, 1450 cm^{-1}
NMR (DMSO-d_6, δ) : 1.02 (3H, d, J=7Hz); 2.25-4.10 (10H, m), 6.91-7.51 (11H, m); 10.74 (1H, d, J=14Hz)
MASS : 320 (M+1)

9) (3R,6S)-1-Benzyl-3-(1H-indol-3-yl-methyl)-6-methylpiperazine

$[\alpha]_D^{19}$: +30.0° (C=1.0, MeOH)
IR (Neat) : 3400, 3125, 1450, 1330 cm^{-1}
NMR (DMSO-d_6, δ) : 1.02 (3H, d, J=7Hz); 2.10-4.10 (10H, m); 6.91-7.47 (10H, m); 10.76 (1H, s)
MASS : 320 (M+1)

10) (2S)-1-Benzyl-2-(2-naphthylmethyl)piperazine

$[\alpha]_D^{19}$: +0.9° (C=1.0, $CHCl_3$)
IR (Neat) : 2600-3100, 1650, 1600 cm^{-1}
NMR ($CDCl_3$, δ) : 2.2-4.3 (10H, m); 3.48 (1H, d, J=13.5Hz); 4.16 (1H, d, J=13.5Hz); 7.0-7.9 (12H, m)
MASS : 317 (M+1)

11) (3S)-3-Benzyl-1-(3-phenylpropyl)piperazine

$[\alpha]_D^{20}$: +12.35° (C=1.075, MeOH)
IR (Neat) : 3230, 3020, 2940, 2800 cm^{-1}
NMR (DMSO-d_6, δ) : 1.50-1.95 (4H, m); 2.19 (2H, t, J=7.2Hz); 2.55-3.45 (10H, m); 7.00-7.20 (10H, m)
MASS : 295 (M+1)

Preparation 9

[0122] A solution of N-(tert-butoxycarbonyl)-D-alanine (3 g) in dimethylformamide (5 ml) was added dropwise to a stirred mixture of 60% sodium hydride (1.4 g) in dimethylformamide (5 ml) at ice-bath temperature. After stirring for 30 minutes at the same temperature, benzyl bromide (4.14 ml) was added and then the mixture was stirred for 1 hour at the same temperature and then for 6 hours at room temperature. The reaction mixture was poured into a mixture of dilute hydrochloric acid and ice-water, and extracted with diisopropyl ether. The extract was washed with aqueous sodium bicarbonate solution and brine successively and dried over magnesium sulfate. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on silica gel eluting with a mixture of n-hexane and ethyl acetate (2:1) to give an oily product, which was dissolved in dichloromethane (40 ml). To the solution was added 4N hydrogen chloride in dioxane solution (7 ml) at ice-bath temperature. The resulting mixture was stirred for 1.5 hours at room temperature and then concentrated under reduced pressure to give benzyl (2R)-2-(N-benzylamino)propionate hydrochloride (2.2 g).

$[\alpha]_D^{19}$: +6.6° (C=1.0, MeOH)
IR (Nujol) : 2700, 2600, 2500, 2375, 1740, 1460 cm^{-1}
NMR (DMSO-d_6, δ) : 1.55 (3H, d, J=7Hz); 4.1-4.28 (3H, m); 5.25 (2H, s); 7.4-7.56 (10H, m); 9.8 (1H, br s); 10.25 (1H, br s)
MASS : 270 (M+1) (free)

Preparation 10

[0123] The following compound was obtained according to a similar manner to that of Preparation 9.

[0124] Benzyl (2S) - (N-benzylamino)propionate hydrochloride

IR (Neat) : 3300, 1730, 1450, 1175, 1150 cm^{-1}
NMR ($CDCl_3$, δ) : 1.33 (3H, d, J=7Hz); 3.43 (1H, q, J=7Hz); 3.72 (2H, q, J=14Hz); 5.17 (2H, s); 7.2-7.36 (10H, m)
MASS : 270 (M+1) (free)

Preparation 11

[0125]

1) N,N-Diisopropylethylamine (8.26 ml) was added to a stirred mixture of N-(tert-butoxycarbonyl)-L-naphthylalanine (10.0 g) and benzyl bromide (4.52 ml) in dimethylformamide (100 ml) at 5°C. The mixture was stirred for 4.5 hours at room temperature and then poured into ice-water (500 ml). The desired product was extracted with ethyl ether and the extract was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was triturated with diisopropyl ether to give benzyl (2S)-2-[N-(tert-butoxycarbonyl)amino]-3-(2-naphthyl)propionate (13.4 g).

mp : 90-91°C
IR (Nujol) : 3380, 1735, 1690, 1520, 1320 cm^{-1}

2) A solution of benzyl (2S)-2-[N-(tert-butoxycarbonyl)amino]-3-(2-naphthyl)propionate (5.0 g) in dimethylformamide (50 ml) was added dropwise to a stirred mixture of 60% sodium hydride (0.6 g) and dimethylformamide (50 ml) at ice-bath temperature. After the addition was completed, the reaction mixture was stirred at the same temperature for 30 minutes. Benzyl bromide (1.76 ml) was added and then the whole mixture was stirred for 3.5 hours. Additional benzyl bromide (0.4 ml) was added and then stirred for 2.5 hours. The reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed successively with 1N hydrochloric acid, aqueous sodium bicarbonate solution and brine and dried over magnesium sulfate. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on silica gel eluting with a mixture of n-hexane and ethyl acetate (4:1) to give benzyl (2S)-2-[N-(tert-butoxycarbonyl)-N-benzylamino]-3-(2-naphthyl)propionate (3.53 g).

IR (Neat) : 3100-2800, 1740, 1690, 1600 cm^{-1}
NMR ($CDCl_3$, δ) : 1.1-1.5 (9H, m); 3.2-4.6 (5H, m); 4.9-5.1 (2H, m); 6.9-7.9 (17H, m)

Preparation 12

[0126] To a mixture of N^2-(tert-butoxycarbonyl)-N^1-formyl-D-tryptophan (2.17 g) and benzyl (2R)-2-(N-benzylamino) propionate hydrochloride (2.0 g) in dichloromethane (30 ml) was added triethylamine (2.3 ml) under nitrogen atmosphere. To the mixture was added 2-chloro-1-methylpyridinium iodide (1.84 g) at room temperature, and the resulting mixture was stirred for 2 hours and left overnight. The reaction mixture was washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was dissolved in dichloromethane (30 ml). A solution of 4N hydrogen chloride in dioxane solution (10 ml) was added thereto at ice-bath temperature and then the resulting mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between dichloromethane and aqueous saturated sodium bicarbonate solution. The organic layer was separated, washed with brine, dried over magnesium sulfate and filtered. To the filtrate was added triethylamine (1 ml) and the resulting mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified on a silica gel column (60 g) eluting with a mixture of n-hexane and ethyl acetate (2:1) to give (3R,6R)-1-benzyl-3-(N-formyl-1H-indol-3-yl-methyl)-6-methylpiperazine-2,5-dione (1.3 g).

IR (Neat) : 3200, 1700, 1675, 1650, 1460 cm^{-1}
NMR (DMSO-d_6, δ) : 0.64 (3H, d, J=7Hz); 3.09-4.83 (6H, m); 7.1-8.4 (10H, m)
MASS : 376 (M+1)

Preparation 13

[0127] The following compound was obtained according to a similar manner to that of Preparation 12.
[0128] (3R, 6S)-1-Benzyl-3-(N-formyl-1H-indol-3-yl-methyl)-6-methylpiperazine-2,5-dione

IR (Neat) : 3200, 1675, 1450, 1370, 1320 cm^{-1}
NMR (DMSO-d_6, δ) : 1.26 (3H, d, J=7Hz); 3.08-3.44 (3H, m); 3.94-4.04 (1H, m); 4.52-4.64 (1H, m); 4.97-5.10 (1H, m); 6.83-7.81 (10H, m); 8.37 (1H, s)
MASS : 376 (M+1)

Preparation 14

[0129] Benzyl (2S)-2-[N-(tert-butoxycarbonyl)-N-benzylamino]-3- (2-naphthyl)propionate (10.5 g) was dissolved in methanol (100 ml) and aqueous 1N sodium hydroxide solution (20 ml) was added at ice-bath temperature. The mixture was stirred at room temperature overnight. The reaction mixture was poured into ice-water and extracted with diisopropyl ether. The aqueous layer was adjusted to pH 3 by adding dilute hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. Evaporation of the solvent gave N-benzyl-N-(tert-butoxycarbonyl)-3-(2-naphthyl)-L-alanine (3.0 g).

NMR ($CDCl_3$, δ) : 1.4-1.6 (9H, m); 3.2-4.6 (5H, m); 5.6-6.4 (1H, br s); 6.7-7.8 (12H, m)
MASS : 404 (M-1)

Preparation 15

[0130] To a stirred mixture of N-benzyl-N-(tert-butoxycarbonyl)-3-(2-naphthyl)-L-alanine (2.9 g), glycine methyl ester hydrochloride (0.9 g) and 1-hydroxybenzotriazole hydrate (1.06 g) in dichloromethane (50 ml) was added dropwise 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (1.43 ml) at ice-bath temperature. The resulting mixture was stirred at room temperature for 2 days and then evaporated under reduced pressure. The residue was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The organic layer was separated, washed with dilute hydrochloric acid and brine, and dried over magnesium sulfate. Evaporation of the solvent gave (2S)-2-[N-benzyl-N-(tert-butoxycarbonyl)amino]-N-methoxycarbonylmethyl-3-(2-naphthyl)propanamide.

IR (Neat) : 3350, 3100-2800, 1750, 1680, 1660, 1600, 1530 cm^{-1}
NMR ($CDCl_3$, δ) : 1.3-1.5 (9H, m); 3.2-4.7 (8H, m); 3.69 (3H, s); 6.8-7.9 (12H, m)
MASS : 477 (M+1), 421, 337

Preparation 16

[0131] To a stirred solution of the object compound of Preparation 15 (3.1 g) in dichloromethane (30 ml) was added dropwise 4N hydrogen chloride in dioxane solution (30 ml) at ice-bath temperature. The resulting mixture was stirred at room temperature for 1 hour and then evaporated under reduced pressure to give an oil, which was partitioned between ethyl acetate and aqueous sodium bicarbonate solution. The ethyl acetate layer was washed with brine and dried over magnesium sulfate. Evaporation of the solvent in vacuo gave a syrup, which was dissolved in a mixture of acetic acid (25 ml) and toluene (25 ml). The resulting mixture was heated at reflux temperature for 3 hours and concentrated under reduced pressure. The residue was triturated with a mixed solvent of water and diisopropyl ether to afford (2S)-1-benzyl-2-(2-naphthylmethyl)piperazine-3,6-dione (1.6 g).

mp : 160-161°C
$[\alpha]_D^{19}$: +0.7° (C=1.0, MeOH)
IR (Nujol) : 3250, 1670, 1650, 1430, 1350 cm^{-1}
NMR (DMSO-d_6, δ) : 2.5-2.6 (2H, m); 3.1-3.5 (2H, m); 4.03 (1H, t, J=4.8Hz); 4.11 (1H, d, J=15.1); 5.16 (1H, d, J=15.1Hz); 7.2-8.0 (12H, m); 8.09 (1H, br s)
MASS : 345 (M+1)

Preparation 17

[0132] A solution of di-tert-butyl dicarbonate (218 mg) in acetone (2 ml) was added dropwise to a stirred mixture of (3R)-1-benzyl-3-(1H-indol-3-yl-methyl)piperazine (305 mg) and triethylamine (150 mg) in a mixed solvent of acetone (3 ml) and water (3 ml) at ice-bath temperature. The resulting mixture was stirred at room temperature for 1 hour and evaporated under reduced pressure. The residue was partitioned between ethyl acetate and water. The organic layer was separated, washed successively with dilute hydrochloric acid, aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. After evaporation of the solvent in vacuo, the residue was dissolved in ethanol (10 ml) and then treated with ammonium formate (315 mg) in the presence of 10% Pd charcoal at 90°C under nitrogen atmosphere. After stirring for 30 minutes, the reaction mixture was filtered and concentrated under reduced pressure to give (2R)-1-(tert-butoxycarbonyl)-2-(1H-indol-3-yl-methyl)piperazine (310 mg).

IR (Neat) : 3300, 1660, 1410 cm^{-1}
NMR (DMSO-d_6, δ) : 1.1 (9H, s); 2.4-4.4 (9H, m); 6.9-7.6 (5H, m); 10.8 (1H, s)
MASS : 316 (M+1)

Preparation 18

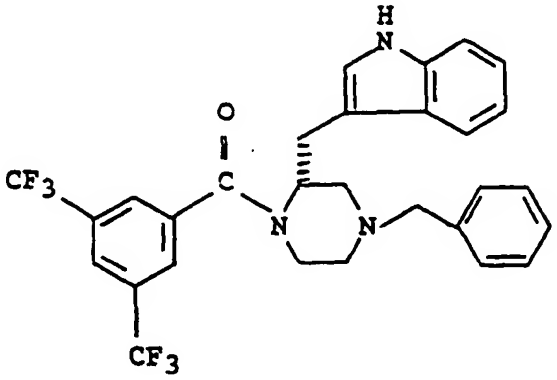
[0133] To a stirred mixture of (2R)-1-(tert-butoxycarbonyl)-2-(1H-indol-3-yl-methyl)piperazine (250 mg) and potassium carbonate (165 mg) in dimethylformamide (1 ml) was added trans-cinnamoyl chloride (150 mg) at room temperature. The resulting mixture was stirred for 3 hours and then poured into water. Extraction with ethyl acetate followed by drying over magnesium sulfate and evaporation in vacuo gave a syrup, which was dissolved in dichloromethane (2 ml). A solution of 4N hydrogen chloride in dioxane solution (1 ml) was added to the solution at ice-bath temperature and the resulting mixture was stirred for 1 hour at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was partitioned between ethyl acetate and aqueous saturated sodium bicarbonate solution. The organic layer was separated, washed with brine and dried over magnesium sulfate. Evaporation of the

solvent in vacuo gave (3R)-1-(transcinnamoyl)-3-(1H-indol-3-yl-methyl)piperazine (166 mg).

$[\alpha]_D^{26}$: -37.5° (C=1.0, MeOH)
IR (Neat) : 3250, 1640, 1590, 1435 cm^{-1}
NMR (DMSO-d_6, δ) : 2.3-4.4 (9H, m); 6.9-7.7 (13H, m); 10.9 (1H, s)
MASS : 346 (M+1)

Example 1

[0134]



[0135] To a mixture of 3,5-bis(trifluoromethyl)benzoic acid (1.15 g) and (3R)-1-benzyl-3-(1H-indol-3-yl-methyl)piperazine (1.61 g) in dichloromethane (80 ml) was added triethylamine (1.55 ml) at room temperature under nitrogen atmosphere. 2-Chloro-1-methylpyridinium iodide (1.37 g) was added, and the mixture was stirred at room temperature for 2.5 hours. The resulting mixture was poured into water (20 ml). The organic layer was washed successively with 0.5N hydrochloric acid, water, aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. After evaporation under reduced pressure, the residue was chromatographed on silica gel with toluene - ethyl acetate (4:1) as an eluent to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.87 g) as a syrup.

IR ($CHCl_3$) : 3430, 3300, 3000, 2910, 2800, 1630-1610 cm^{-1}
NMR (DMSO-d_6, δ) : 1.90-2.40 (2H, m); 2.70-3.90 (8H, m); 4.25-4.40 and 4.75-4.90 (1H, m); 6.50-7.45 (10H, m); 7.50-8.25 (3H, m); 10.77 (1H, s)
MASS : 546 (M+1)

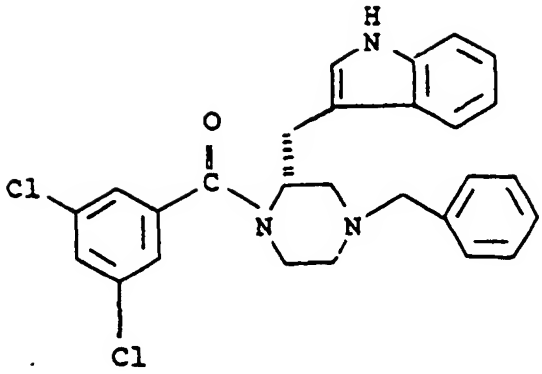
Example 2

[0136] The following compounds were obtained according to a similar manner to that of Example 1.
2) (2R)-4-Benzyl-1-(3,5-dimethylbenzoyl)-2-(1H-indol-3-yl-methyl)piperazine

IR (Nujol) : 3200, 1600 cm^{-1}
NMR (DMSO-d_6, δ) : 1.95-4.40 (9H, m); 2.17 (6H, s); 6.6-7.7 (13H, m); 10.74 (1H, s)
MASS : 438 (M+1)

Example 3

[0137]



[0138] To an ice-cooled mixture of (3R)-1-benzyl-3-(1H-indol-3-yl-methyl)piperazine (305 mg) and potassium carbonate (207 mg) in dimethylformamide (1 ml) was added 3,5-dichlorobenzoyl chloride (210 mg). The mixture was stirred at room temperature for 1 hour. Ethyl acetate and water were added. The organic layer was washed successively with aqueous sodium bicarbonate solution and brine and dried over magnesium sulfate. After evaporation of the solvent, the residue was dissolved in ethyl ether. After insoluble material was removed by filtration, the filtrate was concentrated under reduced pressure and the residue was triturated with diisopropyl ether, collected by filtration and dried to give (2R)-4-benzyl-1-(3,5-dichlorobenzoyl)-2-(1H-indol-3-yl-methyl)piperazine.

mp : 93-98°C
IR (Nujol) : 3225, 1600 cm^{-1}
NMR (DMSO-d_6, δ) : 1.9-4.8 (9H, m); 6.7-7.8 (13H, m); 10.79 (1H, s)
MASS : 478 (M+1)

Example 4

[0139] The following compounds were obtained according to a similar manner to that of Example 3.

1) (2R)-4-Benzyl-1-benzoyl-2-(1H-indol-3-yl-methyl)piperazine

mp : 165-167°C
IR (Nujol) : 3200, 1600, 1440, 1425 cm^{-1}
NMR (DMSO-d_6, δ) : 1.9-4.8 (9H, m); 6.5-7.7 (15H, m); 10.7 (1H, s)
MASS : 410 (M+1)

2) (2R)-4-Benzyl-1-benzenesulfonyl-2-(1H-indol-3-yl-methyl)piperazine

mp : 120-123°C
IR (Nujol) : 3560, 3450, 3225, 1310, 1160 cm^{-1}
NMR (DMSO-d_6, δ) : 1.6-1.9 (2H, m); 2.5-2.8 (2H, m); 3.16-4.03 (5H, m); 6.72-7.83 (15H, m); 10.76 (1H, s)
MASS : 446 (M+1)

4) (2S)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

IR (Neat) : 3275, 1625, 1430 cm^{-1}
NMR (DMSO-d_6, δ) : 1.9-4.8 (11H, m); 6.6-8.4 (13H, m); 10.8 (1H, m)
MASS : 546 (M+1)

5) (2R)-4-Benzyl-1-[2,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 186-187°C
IR (Nujol) : 3200, 1625, 1330, 1310 cm^{-1}
NMR (DMSO-d_6, δ) : 1.8-4.9 (11H, m); 6.6-8.2 (13H, m); 10.7-10.9 (1H, m)
MASS : 546 (M+1)

6) (2R)-4-Benzyl-1-[2,4-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

IR (Neat) : 3250, 1620, 1340 cm^{-1}
NMR (DMSO-d_6, δ) : 2.6-4.9 (11H, m); 6.6-8.3 (13H, m); 10.8-10.9 (1H, m)
MASS : 546 (M+1)

7) (2R)-4-Benzyl-1-(3-phenoxybenzoyl)-2-(1H-indol-3-yl-methyl)piperazine

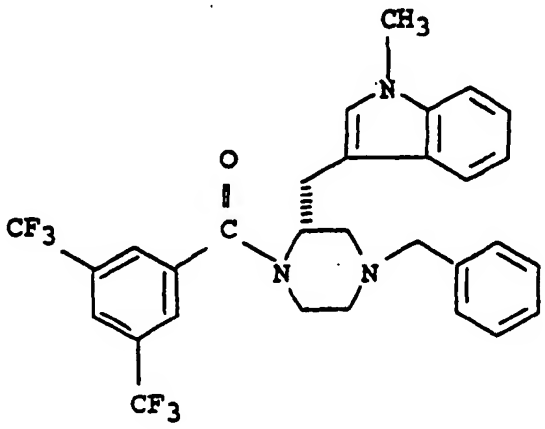
mp : 165-167°C
IR (Nujol) : 3200, 1600, 1450 cm^{-1}
NMR (DMSO-d_6, δ) : 1.9-4.8 (11H, m); 6.7-7.8 (19H, m); 10.7 (1H, s)
MASS : 502 (M+1)

8) (2R)-4-Benzyl-1-[2,6-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

IR (Neat) : 3300, 1640, 1590, 1430 cm^{-1}
NMR (DMSO-d_6, δ) : 1.7-3.6 (11H, m); 6.8-8.4 (13H, m); 10.8 (1H, s)
MASS : 546 (M+1)

Example 5

[0140]

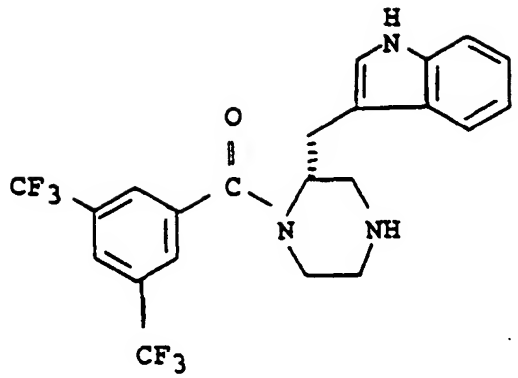


[0141] To an ice-cooled solution of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (1.15 g) in dimethylformamide (60 ml) was added 60% sodium hydride (0.1 g) under nitrogen atmosphere, and the mixture was stirred for 5 minutes. After addition of methyl iodide (0.13 ml), the reaction mixture was stirred for 40 minutes. The reaction was quenched with 0.5N hydrochloric acid (60 ml) and diluted with dichloromethane (80 ml). The organic layer was washed with water, aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. After removal of the solvent, the residue was purified on a silica gel column eluting with a mixture of toluene and ethyl acetate (10:1) to give (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(N-methyl-1H-indol-3-yl-methyl) piperazine (1.12 g) as a syrup.

IR ($CHCl_3$) : 3010, 2930, 2800, 2760, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 1.88-2.35 (2H, m); 2.59-3.15 (4H, m); 3.15-3.48 (2H, m); 3.58 and 3.64 (3H, 2 s); 3.48-3.80 (2H, m); 4.28-4.44 and 4.67-4.85 (1H, 2 m); 6.50-7.48 (10H, m); 7.20, 7.99, 8.06 and 8.20 (3H, 4 m)
MASS : 560 (M+1)

Example 6

[0142]



[0143] A mixture of (2R)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (5.20 g), ammonium formate (1.50 g) and 10% Pd charcoal (0.52 g) in ethanol (50 ml) was refluxed for 7.5 hours under nitrogen atmosphere. The reaction mixture was cooled to room temperature and filtered through Celite pad. The filtrate was concentrated under reduced pressure and the residue was purified on a silica gel column eluting with a mixture of dichloromethane and methanol (20:1) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine (2.67 g, 61.5%) as a syrup.

IR ($CHCl_3$) : 3280, 2900, 1622 cm-1
NMR (DMSO-d_6, δ) : 2.50-3.50 (9H, m); 3.6-4.8 (1H, m); 6.55-7.40 (5H, m); 7.50-8.22 (3H, m); 10.84 (1H, s)
MASS : 456 (M+1)

Example 7

[0144] The following compounds were obtained according to a similar manner to that of Example 6.

2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(N-methyl-1H-indol-3-yl-methyl)piperazine

IR ($CHCl_3$) : 3320, 2940, 2830, 1628 cm^{-1}
NMR (DMSO-d_6, δ) : 2.50-3.59 (9H, m); 3.69, 3.70 (3H, s); 4.15-4.35, 4.65-4.84 (1H, m); 6.64-8.22 (8H, m)
MASS : 470 (M+1)

3) (2R)-1-Benzoyl-2-(1H-indol-3-yl-methyl)piperazine

mp : 211-213°C
$[\alpha]_D^{25}$: +51.4° (C=1.0, MeOH)
IR (Nujol) : 3200, 1600, 1590 cm^{-1}
NMR (DMSO-d_6, δ) : 2.5-4.7 (9H, m); 6.6-7.9 (10H, m); 10.8 (1H, s)
MASS : 320 (M+1)

4) (2R)-1-Benzenesulfonyl-2-(1H-indol-3-yl-methyl)piperazine

mp : 152-154°C
$[\alpha]_D^{25}$: -1.7° (C=1.0, MeOH)
IR (Nujol) : 3350, 1290, 1150 cm^{-1}
NMR (DMSO-d_6, δ) : 2.25-3.60 (8H, m); 3.95-4.0 (1H, m); 6.96-7.84 (10H, m); 10.86 (1H, s)
MASS : 355 (M+1)

5) (2R)-1-(3,5-Dimethylbenzoyl)-2-(1H-Indol-3-ylmethyl)piperazine

$[\alpha]_D^{25}$: +44.4° (C=1.0, MeOH)
IR (Neat) : 3225, 1600, 1430, 1330 cm^{-1}
NMR (DMSO-d_6, δ) : 2.18 (6H, s); 2.5-4.8 (9H, m); 6.55-7.34 (8H, m); 10.85 (1H, s)
MASS : 348 (M+1)

6) (2R)-1-(3,5-Dichlorobenzoyl)-2-(1H-indol-3-ylmethyl)piperazine

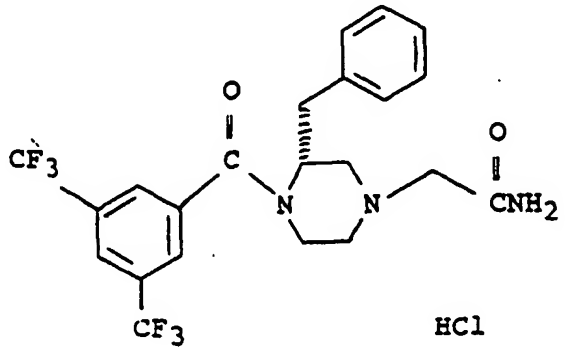
$[\alpha]_D^{25}$: +34.7° (C=1.0, MeOH)
IR (Nujol) : 3200, 1620, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 2.9-4.5 (9H, m); 6.7-7.5 (9H, m); 10.96 (1H, s)
MASS : 388 (M+1), 354, 320

8) (2S)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

IR (Neat) : 3250, 1625, 1430 cm^{-1}
NMR (DMSO-d_6, δ) : 2.6-4.9 (9H, m); 6.6-8.2 (8H, m); 8.4 (1H, s); 10.9 (1H, s)
MASS : 456 (M+1)

Preparation Example 9 (not within the scope of the invention)

[0145]

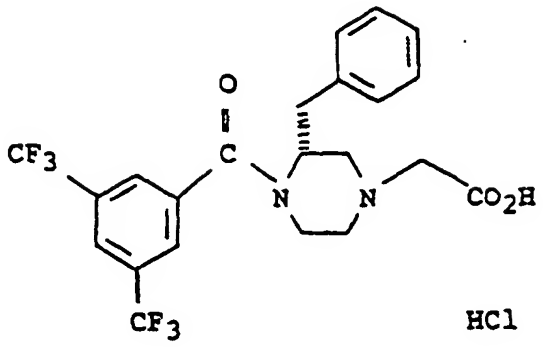


[0146] (2R)-2-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(methoxycarbonylmethyl)piperazine (0.2 g) was treated with 20% ammonia methanol solution (5 ml), and the resulting mixture was left overnight in a refrigerator. The reaction mixture was concentrated under reduced pressure and the residue was purified on a silica gel column (7 g) eluting with a mixture of dichloromethane and methanol (10:1) to give (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(carbamoylmethyl)piperazine. This compound was treated with 4N hydrogen chloride in ethyl acetate solution to give the corresponding hydrochloride (0.18 g) as a white powder.

mp : 166-169°C
$[\alpha]_D^{26}$: -6.4° (C=1.0, MeOH)
IR (Nujol) : 3600-3050, 2700-2000, 1685, 1635, 1275, 1128, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.70-5.15 (13H, m); 6.90-7.00 (1H, m); 7.10-7.50 (5H, m); 7.65-7.85 (1H, m); 8.10-8.25 (1H, m)

Preparation Example 10 (not within the scope of the invention)

[0147]

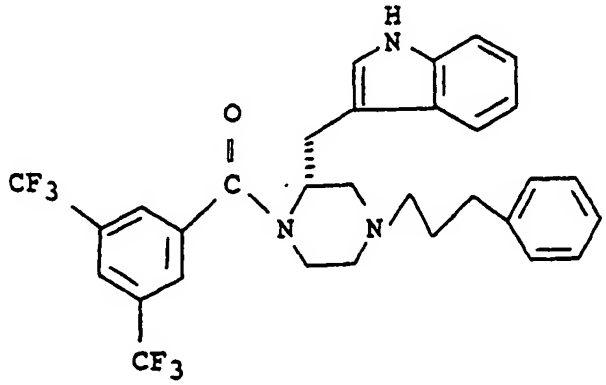


[0148] To a solution of (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(methoxycarbonylmethyl)piperazine (0.18 g) in methanol (18 ml) was added aqueous 1N sodium hydroxide solution (4.3 ml), and the mixture was stirred at room temperature for 50 minutes. The reaction mixture was evaporated under reduced pressure and the residue was diluted with water (4 ml). 1N Hydrochloric acid (4.3 ml) was added to the solution at 0°C and the resulting precipitate was collected by filtration and washed with water. The obtained carboxylic acid was converted to the corresponding hydrochloride by treatment with 4N hydrogen chloride in ethyl acetate solution to give (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(carboxymethyl)piperazine hydrochloride (0.12 g).

mp : 158-161°C
$[\alpha]_D^{25}$: -11.5° (C=1.0, MeOH)
IR (Nujol) : 3650-3100, 2700-2100, 1730, 1630, 1276, 1130, 903 cm^{-1}
NMR (DMSO-d_6, δ) : 2.70-5.15 (11H, m); 6.90-8.25 (8H, m)
MASS : 475 (M+1) (free), 417

Example 11

[0149]



[0150] A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.17 g), 1-bromo-3-phenylpropane (0.08 g) and potassium carbonate (0.15 g) in dry dimethylformamide (10 ml) was stirred at room temperature under nitrogen atmosphere. After 2 hours, additional 1-bromo-3-phenylpropane (0.14 ml) and potassium carbonate (0.15 g) were added, and the mixture was stirred overnight. Water (50 ml) and dichloromethane (50 ml) were added to the mixture. The dichloromethane layer was washed with brine and dried over magnesium sulfate. After

evaporation of the solvent, the residue was purified on a silica gel column (10 g) eluting with a mixture of toluene and ethyl acetate (4:1) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(3-phenylpropyl)piperazine (0.17 g) as a syrup.

IR ($CHCl_3$) : 3300, 2930, 1686, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.62-2.44 (6H, m); 2.67 (2H, t); 2.80-3.30 (5H, m); 3.75-4.40, 4.80-4.95 (2H, m); 6.53-7.35 (10H, m); 7.40-8.20 (3H, m); 10.85 (1H, s)
MASS : 574 (M+1)

Example 12

[0151] The following compounds were obtained according to a similar manner to that of Example 11.
15) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-methyl-2-(N-methyl-1H-indol-3-yl-methyl)piperazine

IR ($CHCl_3$) : 2930, 2830, 2780, 1683 cm^{-1}
NMR (DMSO-d_6, δ) : 1.78-2.44 (2H, m); 2.24 (3H, s); 2.64-3.97 (6H, m); 3.69 and 3.72 (3H, 2 s); 4.17-4.96 (1H, m); 6.64-8.30 (8H, m)
MASS : 484 (M+1)

Preparation Example 14 (not within the scope of the invention)

[0152] To an ice-cooled mixture of (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]piperazine (0.3 g) and triethylamine (0.39 ml) in dimethylformamide (8 ml) was added 3-(chloromethyl)pyridine hydrochloride (0.12 g). The reaction mixture was stirred at the same temperature for 30 minutes and then at room temperature for 2 hours. Additional triethylamine (0.39 ml) and 3-(chloromethyl)pyridine hydrochloride (0.12 g) were added and the resulting mixture was stirred overnight. The reaction-mixture was filtered and the filtrate was concentrated and subjected to a chromatography on a silica gel eluting with a mixture of toluene and ethyl acetate (5:1). The eluent was treated with 4N hydrogen chloride in ethyl acetate solution to give (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(pyridin-3-yl-methyl)piperazine dihydrochloride.

mp : 164-168°C
$[\alpha]_D^{25}$: +9.1° (C=1.0, MeOH)
IR (Nujol) : 3700-3100, 2700-2000, 1630, 1270, 1120, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.80-5.40 (11H, m); 6.85-6.90 (1H, m); 7.10-7.40 (4H, m); 7.46 (1H, s); 7.75 (1H, s); 7.90-8.00 (1H, m); 8.19-8.23 (1H, m); 8.66-8.70 (1H, m); 8.88-8.91 (1H, m); 9.09 (1H, s)

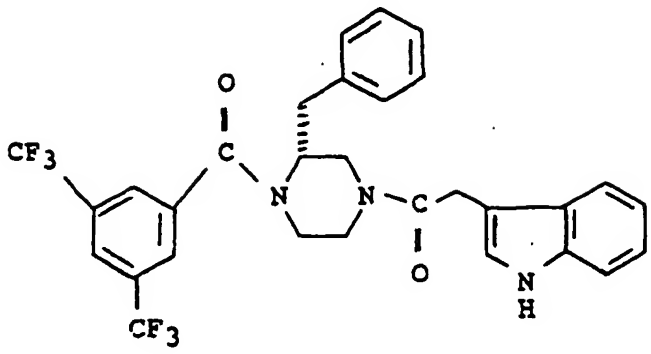
Example 15

[0153] The following compounds were obtained according to a similar manner to that of Preparation Example 14.
2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(methoxycarbonylmethyl)piperazine

$[\alpha]_D^{24}$: -8.3° (C=1.0, MeOH)
IR (Neat) : 3300, 1737, 1628, 1276, 1130, 900, 737 cm^{-1}
NMR (DMSO-d_6, δ) : 2.30-5.00 (14H, m); 6.60-8.20 (8H, m); 10.87 (1H, s)
MASS : 528 (M+1)

Preparation Example 16 (not within the scope of the invention)

[0154]



[0155] To a stirred mixture of (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]piperazine (0.3 g) and 2-(1H-indol-3-yl)acetic acid (0.13 g) in dichloromethane (8 ml) containing triethylamine (0.25 ml) was added 2-chloro-1-methylpyridinium iodide (0.22 g) at room temperature under nitrogen atmosphere. After being stirred for 5 hours, the reaction mixture was diluted with dichloromethane and washed with 0.1N hydrochloric acid, aqueous saturated sodium bicarbonate solution and brine, and dried over magnesium sulfate. After removal of the solvent, the residue was purified by column chromatography on silica gel using chloroform-methanol (50:1) as eluent to give (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[2-(1H-indol-3-yl)acetyl]piperazine (0.34 g) as a white powder.

mp : 201-210°C
$[\alpha]_D^{27}$: +27.6° (C=1.0, MeOH)
IR (Nujol) : 3270, 1630, 1276, 1115, 900, 737 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-5.00 (11H, m); 6.70-7.70 (12H, m); 8.10-8.20 (1H, m); 10.85-11.10 (1H, m)
MASS : 574 (M+1), 417

Example 17

[0156] The following compounds were obtained according to a similar manner to that of Preparation Example 16.

1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(trans-cinnamoyl)piperazine

mp : 118-119°C
$[\alpha]_D^{25}$: -34.7° (C=1.0, MeOH)
IR (Nujol) : 3550-3100, 1635, 1275, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.80-5.20 (11H, m); 6.50-8.20 (14H m)
MASS : 586 (M+1), 452

3) (2R)-1-[3,5-Bis(trifluromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[2-(N,N-dimethylamino)acetyl]piperazine

IR (Nujol) : 3200, 1655, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 2.10-2.50 (6H, m); 2.74-4.65 and 4.80-5.15 (11H, 2 m), 6.54-7.55 (5H, m); 7.60-8.30 (3H, m); 10.92 (1H, s)
MASS : 541 (M+1)

36) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(3-cyclohexylpropionyl)piperazine

mp : 190-192°C
$[\alpha]_D^{26}$: -4.5° (C=1.0, MeOH)
IR (Nujol) : 3280, 1649, 1627, 1276, 1170, 1130, 898 cm^{-1}
NMR (DMSO-d_6, δ) : 0.60-1.80 (11H, m); 2.20-5.20 (13H, m); 6.60-8.30 (8H, m); 10.88 (1H, s)

MASS : 594 (M+1)

49) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-(3-cyclopentylpropionyl)-2-(1H-indol-3-yl-methyl)piperazine

mp : 180-183°C
$[\alpha]_D^{20}$: -2.9° (C=1.0, MeOH)
IR (Nujol) : 3280, 1650, 1628, 1277, 1212, 1170, 1131, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 0.85-1.35 (2H, m); 1.40-2.00 (9H, m); 2.20-5.15 (11H, m); 6.60-8.25 (8H, m); 10.88 (1H, s)
MASS : 580 (M+1)

50) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[(3-cyclohexyl)-trans-acryloyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 198-200°C
$[\alpha]_D^{24}$: -19.0° (C=0.1, MeOH)
IR (Nujol) : 3280, 1655, 1628, 1275, 1170, 1132, 900, 750 cm^{-1}
NMR (DMSO-d_6, δ) : 0.65-1.25 (5H, m); 1.35-2.15 (6H, m); 2.55-5.00 (9H, m); 5.85-8.10 (10H, m); 10.60-10.80 (1H, m)
MASS : 592 (M+1)

51) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-(4-fluorobenzoyl)-2-(1H-indol-3-yl-methyl)piperazine

mp : 164-165°C
IR (Nujol) : 3280, 1626, 1510 cm^{-1}
NMR (DMSO-d_6, δ) : 2.55-5.05 (9H, m); 6.45-8.25 (12H, m); 10.84 (1H, s)
MASS : 578 (M+1)

54) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(3-pyridyl)carbonyl]piperazine hydrochloride

mp : 150-160°C
$[\alpha]_D^{24}$: +1.7° (C=1.0, MeOH)
IR (Nujol) : 3650-3100, 2800-2000, 1625, 1280, 1180, 1127, 903 cm^{-1}
NMR (DMSO-d_6, δ) : 2.80-5.20 (9H, m); 6.40-9.20 (12H,m)
MASS : 561 (M+1) (free)

55) (2R)-4-[2-(Benzoylamino)acetyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 123-135°C
$[\alpha]_D^{24}$: -6.6° (C=0.5, MeOH)
IR (Nujol) : 3600-3100, 1636, 1278, 1175, 1133, 903 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-5.20 (11H, m); 6.55-8.21 (13H, m); 8.65-8.75 (1H, m); 10.80-11.00 (1H, m)
MASS : 617 (M+1), 456

56) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-(cyclopropylcarbonyl)-2-(1H-indol-3-yl-methyl)piperazine mp : 109-114°C

$[\alpha]_D^{20}$: -8.2° (C=1.0, MeOH)
IR (Nujol) : 3500-3100, 1630, 1276, 1175, 1130, 902 cm^{-1}
NMR (DMSO-d_6, δ) : 0.78 (4H, br s), 2.60-5.20 (10H, m); 6.60-8.25 (8H, m); 10.87 (1H, s)
MASS : 524 (M+1)

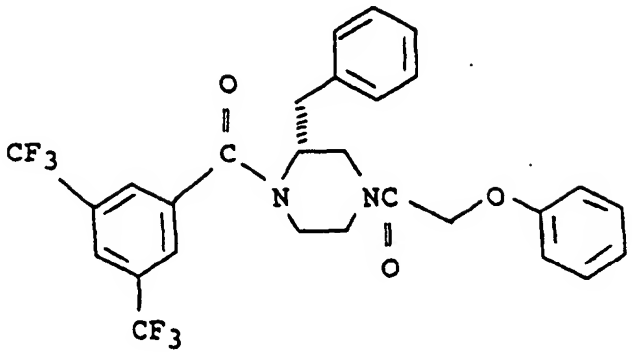
57) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[3-(3-pyridyl)-trans-acryloyl]piperazine

mp : 86.5-89.5°C
$[\alpha]_D^{24}$: -25.0° (C=1.0, MeOH)
IR (Nujol) : 3600-3100, 1637, 1278, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.70-5.20 (9H, m); 6.15-8.35 (12H, m); 8.50-8.62 (1H, m); 8.75-9.05 (1H, m); 10.85-10.90 (1H, m)

MASS : 587 (M+1), 457

Preparation Example 18 (not within the scope of the invention)

[0157]



[0158] To a stirred solution of (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]piperazine (0.3 g) in dry dimethylformamide (3 ml) containing dry pyridine (0.06 ml) was added a solution of 2-phenoxyacetyl chloride (0.12 g) in dry dimethylformamide (1 ml) at 0°C, and the mixture was stirred at the same temperature for 30 minutes and then at room temperature for 30 minutes. Additional pyridine (0.02 ml) and a solution of 2-phenoxyacetyl chloride (0.025 g) in dry dimethylformamide (0.3 ml) were added to the reaction mixture. After being stirred for 30 minutes, the mixture was poured into water (43 ml) and extracted with ethyl acetate. The extract was washed with brine and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by a silica gel column chromatography. Elution with toluene - ethyl acetate afforded (2R)-2-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(2-phenoxyacetyl)piperazine (0.34 g) as a white powder.

$[\alpha]_D^{25}$: +28.9° (C=1.0, MeOH)
IR (Neat) : 3700-3100, 1635, 1274, 1170, 1126, 900, 748 cm^{-1}
NMR (DMSO-d_6, δ) : 2.80-5.20 (11H, m); 6.90-7.70 (12H, m); 8.12-8.22 (1H, m)
MASS : 551 (M+1), 417

Example 19

[0159] The following compounds were obtained according to a similar manner to that of Preparation Example 18.

1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(N,N-dimethylaminocarbonyl)piperazine

IR (Nujol) : 3230, 1621 cm^{-1}
NMR (DMSO-d_6, δ) : 2.73 (1H, s); 2.82 (6H, s); 2.89 (1H, s); 2.70-4.98 (7H, m); 6.55-7.40 (5H, m); 7.40-8.24 (3H, m); 10.86 (1H, s)
MASS : 527 (M+1)

12) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-propionylpiperazine

mp : 177-178°C
$[\alpha]_D^{22}$: -8.7° (C=1.0, MeOH)
IR (Nujol) : 3300, 1635, 1282, 1224, 1124, 905, 748 cm^{-1}
NMR (DMSO-d_6, δ) : 0.90-1.15 (3H, m); 2.20-5.15 (11H, m); 6.75-8.25 (8H, m); 10.87 (1H, s)
MASS : 512 (M+1)

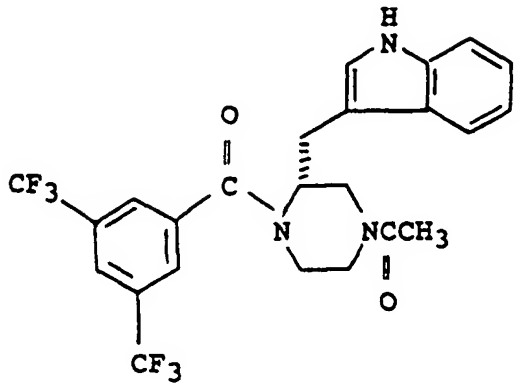
13) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-mesylpiperazine

mp : >225°C

$[\alpha]_D^{21}$: +20.6° (C=1.0, DMF)
IR (Nujol) : 3390, 1634, 1318, 1280, 1139, 964, 898, 747 cm^{-1}
NMR (DMSO-d_6, δ) : 2.80-5.10 (12H, m); 6.55-8.25 (8H, m); 10.91 (1H, s)
MASS : 534 (M+1), 456

Example 20

[0160]



[0161] To a stirred mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.15 g) and potassium carbonate (0.14 g) in dimethylformamide (10 ml) was added acetyl chloride (0.04 ml) at room temperature. After being stirred for 3 hours, the reaction mixture was quenched with water (50 ml) and extracted with dichloromethane (50 ml). The organic layer was washed with aqueous sodium bicarbonate solution and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified on a silica gel column (10 g) eluting with a mixture of dichloromethane and methanol (20:1). The fractions containing object compound were collected and evaporated under reduced pressure. To the resulting oily product was added a mixed solvent of ethyl ether and diisopropyl ether, and the mixture was concentrated under reduced pressure. The obtained powder was collected by filtration and dried in vacuo to give (2R)-4-acetyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.09 g) as a powder.

IR ($CHCl_3$) : 3270, 2990, 2900, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.9-2.2 (3H, m); 2.73 (1H, s); 2.89 (1H, s); 2.65-3.12 (3H, m); 3.15-3.48 (1H, m), 3.65-4.10 (2H, m); 4.20-4.68 (1H, m); 6.58-7.48 (5H, m); 7.60-8.26 (3H, m); 10.88 (1H, s)
MASS : 498 (M+1)

Example 21

[0162] The following compounds were obtained according to a similar manner to that of Example 20.
1) (2R)-4-Acetyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(N-methyl-1H-indol-3-yl-methyl)piperazine

IR ($CHCl_3$) : 3460, 3000, 2920, 1620 cm^{-1}
NMR (DMSO-d_6, δ) : 1.9-2.2 (3H, m); 2.73 (1H, s); 2.89 (1H, s); 2.68-3.14 (2H, m); 2.68-3.56 (2H, m); 3.71-3.75 (3H, s); 3.60-4.10 (2H, m); 4.10-4.65 (1H, m); 6.60-8.28 (8H, m)
MASS : 512 (M+1)

Example 23

[0163] To a solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.1 g) in dichloromethane (10 ml) was added 4N hydrogen chloride in dioxane solution (0.05 ml) at 0°C. The resulting mixture was stirred at the same temperature for 50 minutes and then concentrated under reduced pressure. The obtained powder was collected by filtration and washed with ethyl ether to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride (0.1 g).

IR (Nujol) : 3340, 1648 cm^{-1}
NMR (DMSO-d_6, δ) : 2.9-3.9 (8H, m); 3.9-5.2 (1H, m); 6.57-7.50 (5H, m); 7.50-8.30 (3H, m); 9.40-10.00 (2H, m); 10.96 (1H, s)
MASS : 456 (M+1) (free)

Example 24

[0164] The following compounds were obtained according to a similar manner to that of Example 23.

1) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3--yl-methyl)piperazine hydrochloride
NMR (DMSO-d_6, δ) : 2.80-4.30 (9H, m); 4.40-4.75 and 4.95-5.15 (2H, 2 m); 6.45-8.30 (13H, m); 10.85 (1H, s); 11.10-11.65 (1H, m)

2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(3-phenylpropyl)piperazine hydrochloride

IR (Nujol) : 3200, 1636 cm^{-1}
NMR (DMSO-d_6, δ) : 2.00-2.25 (2H, m); 2.55-2.77 (2H, m); 2.90-4.16 (11H, m); 6.80-7.48 (10H, m); 7.55-8.28 (3H, m); 10.94 (1H, s); 11.26, 11.40 (1H, br s)
MASS : 574 (M+1) (free)

3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(N-methyl-1H-indol-3-yl-methyl)-4-methylpiperazine hydrochloride

mp : 221-226°C
IR (Nujol) : 3340, 2700, 1624 cm^{-1}
NMR (DMSO-d_6, δ) : 2.78 and 2.82 (3H, 2 s); 2.97-3.83 and 4.00-4.18 (8H, 2 s); 3.71, 3.76 (3H, s); 4.48-4.69 and 4.98-5.16 (1H, 2 m); 6.62-8.29 (8H, m); 11.36, 11.49 (1H, br s)
MASS : 484 (M+1) (free)

4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[2-(N,N-dimethylamino)acetyl]piperazine hydrochloride

IR (Nujol) : 3300-3200, 2700, 1625 cm^{-1}
NMR (DMSO-d_6, δ) : 2.5-2.8 (6H, m); 2.84-4.46 (11H, m); 6.50-8.29 (8H, m); 8.41 and 8.80 (1H, 2 br s); 11.00 (1H, s)
MASS : 541 (M+1) (free)

5) (2R)-4-Benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(N-methyl-1H-indol-3-yl-methyl)piperazine hydrochloride

$[\alpha]_D^{28}$: +13.1° (C=1.0, $CHCl_3$)
IR (Nujol) : 3360, 2550, 1636 cm^{-1}
NMR (DMSO-d_6, δ) : 2.90-3.52 (4H, m); 3.59 and 3.64 (3H, 2 s); 3.52-4.29 (5H, m); 4.47-4.74 and 4.90-5.10 (2H, 2 m); 6.50-8.30 (13H, m)
MASS : 560 (M+1) (free)

10) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(methoxycarbonylmethyl)piperazine hydrochloride

mp : 167-169°C
$[\alpha]_D^{25}$: -30.0° (C=1.0, MeOH)
IR (Nujol) : 3700-3100, 2750-2000, 1749, 1638, 1278, 1175, 1130, 903 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-5.15 (14H, m); 6.60-8.30 (8H, m); 10.97 (1H, s)
MASS : 528 (M+1) (free)

Example 25

[0165] The following compounds were obtained according to a similar manner to that of Preparation Example 9.
2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(carbamoylmethyl)piperazine

mp : 170-173°C
$[\alpha]_D^{20}$: -5.5° (C=1.0, MeOH)
IR (Nujol) : 3550-3000, 1691, 1600, 1276, 1222, 1190, 1130, 902 cm^{-1}
NMR (DMSO-d_6, δ) : 2.00-4.95 (11H, m), 6.60-8.25 (10H, m); 10.86 (1H, s)
MASS : 513 (M+1), 456

Example 26

[0166] A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(methoxycarbonylmethyl)piperazine (0.15 g) and 30% methylamine ethanol solution (5 ml) was left at about 4°C in a refrigerator. After 24 hours, the mixture was evaporated and the residue was chromatographed on a column of silica gel with a mixture of dichloromethane and methanol. The eluates were collected and evaporated. The product was dissolved in ethyl acetate (2 ml) and then treated with 4N hydrogen chloride in ethyl acetate solution to afford (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(N-methylcarbamoylmethyl)piperazine hydrochloride (0.14 g) as a white powder.

mp : 175-180°C
$[\alpha]_D^{21}$: -26.0° (C=1.0, MeOH)
IR (Nujol) : 3700-3100, 2700-2000, 1673, 1635, 1276, 1173, 1131, 903 cm^{-1}
NMR (DMSO-d_6, δ) : 2.69 (3H, s); 2.80-5.10 (11H, m); 6.60-8.80 (9H, m); 10.99 (1H, s)
MASS : 527 (M+1) (free)

Preparation Example 27 (not within the scope of the invention)

[0167] To a stirred mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-(carboxymethyl)piperazine hydrochloride (210 mg), N-methylbenzylamine (52 mg) and triethylamine (0.19 ml) in dichloromethane (5 ml) was added 2-chloro-1-methylpyridinium iodide (110 mg) under nitrogen atmosphere at room temperature. The mixture was stirred at the same temperature for 1 hour. After removal of the solvent, the residue was purified by column chromatography on a silica gel eluting with a mixture of dichloromethane and methanol (10:1). The eluate was concentrated and treated with 4N hydrogen chloride in ethyl acetate solution to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[(N-methyl-N-benzylcarbamoyl)methyl]piperazine hydrochloride (190 mg) as a powder.

mp : 145-149°C (dec.)
$[\alpha]_D^{21}$: -15.2° (C=0.5, MeOH)

Example 29

[0168] The following compounds were obtained according to a similar manner to that of Example 6.
2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-[(1R)-1-(N-methyl-1H-indol-3-yl)ethyl]piperazine

IR (Neat) : 3300, 1730, 1630, 1430 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.5 (3H, m); 2.5-3.6 (7H, m); 3.70 (3H, s); 3.9-4.1 (1H, m); 4.9-5.0 (1H, m); 6.6-7.4 (5H, m); 7.6-8.5 (3H, m)
MASS : 484 (M+1)

Example 30

[0169] The following compounds were obtained according to a similar manner to that of Example 11.

3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-trityl-1-piperazinyl)carbonylmethyl]piperazine

mp : 160-166°C
$[\alpha]_D^{21}$: -23.0° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 1635, 1277, 1175, 1133, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.80-5.00 (19H, m); 6.60-8.20 (23H, m); 10.85 (1H, s)
MASS : 824 (M+1), 580

7) (2R)-4-[4-(Ethoxycarbonyl)butyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

$[\alpha]_D^{20}$: -0.6° (C=0.5, DMF)
IR (Neat) : 3300, 1720, 1620, 1275, 1175, 1125, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.18 (3H, t, J=7.1Hz); 1.30-5.00 (19H, m); 6.60-8.20 (8H, m); 10.85 (1H, s)
MASS : 584 (M+1), 456

8) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[3-(methoxycarbonyl)propyl]piperazine hydrochloride

mp : 133-134°C
$[\alpha]_D^{18}$: +0.8° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 2800-2000, 1725, 1635, 1277, 1173, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.90-5.20 (18H, m); 6.60-8.20 (8H, m); 10.94 (1H, s); 11.10-11.50 (1H, m)
MASS : 556 (M+1) (free)

9) (2R)-4-[3-(Benzyloxycarbonyl)propyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine

$[\alpha]_D^{21}$: -1.8° (C=0.5, DMF)
IR (Neat) : 3550-3100, 1727, 1625, 1274, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.70-2.40 (6H, m); 2.60-5.00 (9H, m); 5.12 (2H, s); 6.60-8.20 (13H, m); 10.85 (1H, s)
MASS : 632 (M+1)

10) (2R)-4-(Benzyloxycarbonylmethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-ylmethyl)piperazine

$[\alpha]_D^{21}$: -11.6° (C=1.0, MeOH)
IR (Neat) : 3600-3100, 1735, 1626, 1275, 1129, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-5.20 (13H, m); 6.60-8.20 (13H, m); 10.85 (1H, br s)
MASS : 604 (M+1), 454

11) (2R)-4-(Benzyloxycarbonylmethyl)-2-(1H-indol-3-ylmethyl)-1-(3,5-dimethylbenzoyl)piperazine

mp : 148-150°C
$[\alpha]_D^{21}$: +40.2° (C=0.5, DMF)
IR (Nujol) : 3200, 1735, 1604, 1149, 734 cm^{-1}
NMR (DMSO-d_6, δ) : 2.10-4.40 (17H, m); 5.13 (2H, s); 6.50-7.80 (13H, m); 10.85 (1H, s)
MASS : 496 (M+1)

12) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[(4-fluorophenyl)carbonylmethyl]-2-(1H-indol-3-ylmethyl)piperazine

mp : 95-105°C
$[\alpha]_D^{17}$: -21.2° (C=0.5, MeOH)
IR (Nujol) : 3450-3100, 1628, 1595, 1277, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-4.95 (11H, m); 6.50-8.20 (12H, m); 10.81 (1H, s)
MASS : 592 (M+1)

Example 31

[0170] The following compounds were obtained according to a similar manner to that of Preparation Example 16.

4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(2-pyrazinyl)carbonyl]piperazine dihydrochloride

mp : 92-95°C
$[\alpha]_D^{22}$: -2.6° (C=0.5, MeOH)
IR (Nujol) : 3600-3100, 2750-2000, 1630, 1276, 1174, 1128, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.80-5.20 (9H, m); 6.15-9.05 (11H, m); 10.78-10.92 (1H, m)
MASS : 562 (M+1) (free), 456

5) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[4-(dimethylamino)benzoyl]piperazine

IR ($CHCl_3$) : 3250, 2990, 2900, 1602, 1522 cm^{-1}
NMR (DMSO-d_6, δ) : 2.97 (6H, s); 2.58-3.60 (6H, m); 3.82-4.96 (3H, m); 6.54-8.26 (12H, m); 10.84 (1H, s)
MASS : 603 (M+1)

6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(4-hydroxybenzoyl)piperazine

mp : >145°C
IR (Nujol) : 3330, 1638, 1600 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-3.67 (6H, m); 3.82-4.99 (3H, m); 6.50-8.24 (12H, m); 9.90 (1H, s); 10.84 (1H, s)
MASS : 576 (M+1)

7) (2R)-4-(4-Acetoxybenzoyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 196-197°C
IR (Nujol) : 3400, 1733, 1625 cm^{-1}
NMR (DMSO-d_6, δ) : 2.30 (3H, s); 3.00-5.05 (9H, m); 6.52-8.28 (12H, m); 10.83 (1H, s)
MASS : 618 (M+1)

8) (2R)-4-(4-Cyanobenzoyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 205-207°C
IR (Nujol) : 3260, 2220, 1626 cm^{-1}
NMR (DMSO-d_6, δ) : 2.76-5.10 (9H, m); 6.44-8.25 (12H, m); 10.80 and 10.88 (1H, 2 s)
MASS : 585 (M+1)

9) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(4-acetylbenzoyl)piperazine

mp : 245-248°C
IR (Nujol) : 3270, 1683, 1638, 1626, 1609 cm^{-1}
NMR (DMSO-d_6, δ) : 2.62 (3H, s); 2.80-5.08 (9H, m); 6.40-8.26 (12H, m); 10.76 and 10.89 (1H, 2 s)
MASS : 602 (M+1)

12) (2R)-4-Benzoyl-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

IR (Nujol) : 3250, 1622 cm^{-1}
NMR (DMSO-d_6, δ) : 2.80-5.05 (9H, m); 6.50-8.25 (13H, m); 10.84 (1H, s)
MASS : 560 (M+1)

13) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(4-nitrobenzoyl)piperazine

mp : 151-153°C
IR (Nujol) : 3330, 1653, 1626, 1520 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-5.10 (9H, m); 6.40-8.40 (12H, m); 10.77 and 10.91 (1H, 2 s)
MASS : 605 (M+1)

15) (2R)-4-(trans-Cinnamoyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-[(1R)-1-(N-methyl-1H-indol-3-yl)ethyl]piperazine

mp : 90-91°C
$[\alpha]_D^{24}$: +0.6° (C=0.5, MeOH)
IR (Nujol) : 1640, 1600, 1450, 1380, 1350 cm^{-1}
NMR ($CDCl_3$, δ) : 1.4-1.7 (3H, m); 2.5-5.3 (8H, m); 3.69 (3H, s); 6.6-7.9 (15H, m)
MASS : 614 (M+1)

17) (2R)-4-(2,2,2-Trifluoroacetyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 197.6-198.8°C
IR (Nujol) : 3300, 1690, 1628, 1610 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-5.20 (9H, m); 6.50-8.25 (8H, m); 10.88 (1H, s)
MASS : 552 (M+1)

18) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-cyclohexylcarbonyl-2-(1H-indol-3-yl-methyl)piperazine

mp : 200-201°C
$[\alpha]_D^{22}$: -3.8° (C=1.0, MeOH)
IR (Nujol) : 3340, 1630, 1617, 1272, 1184, 1136, 902 cm^{-1}
NMR (DMSO-d_6, δ) : 1.00-1.95 (10H, m); 2.40-5.20 (10H, m); 6.55-8.25 (8H, m); 10.80-11.00 (1H, m)
MASS : 566 (M+1)

19) (2R)-4-(2-Chloroacetyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 185-187°C
$[\alpha]_D^{22}$: -0.1° (C=1.0, MeOH)
IR (Nujol) : 3280, 1660, 1630, 1279, 1225, 1190, 1125, 905, 750 cm^{-1}
NMR (DMSO-d_6, δ) : 2.70-5.10 (11H, m); 6.55-8.20 (8H, m); 10.90 (1H, s)
MASS : 532 (M+1), 456

20) (2R)-4-(3,4-Difluoro-trans-cinnamoyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 214-217°C
$[\alpha]_D^{21}$: -30.6°C (C=1.0, MeOH)
IR (Nujol) : 3270, 1625, 1607, 1511, 1276, 1131, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.70-5.20 (9H, m); 6.60-8.25 (13H, m); 10.85 (1H, br s)
MASS : 622 (M+1)

Example 32

[0171] The following compounds were obtained according to a similar manner to that of Preparation Example 27.

2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-methyl-N-(2-dimethylaminoethyl)carbamoylmethyl]piperazine dihydrochloride

mp : 200-205°C
$[\alpha]_D^{21}$: -20.2° (C=0.5, DMF)
IR (Nujol) : 3340, 3180, 2670, 1655, 1275, 1195, 1129, 908 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-5.10 (24H, m); 6.60-8.30 (8H, m); 10.00-10.90 (2H, m); 11.00 (1H, s)
MASS : 598 (M+1) (free)

3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-(2-piperidinoethyl)carbamoylmethyl]piperazine dihydrochloride

mp : 194-201°C
$[\alpha]_D^{22}$: -9.6° (C=0.5, DMF)
IR (Nujol) : 3680-3100, 2750-1970, 1680, 1635, 1274, 1170, 1125, 902 cm^{-1}
NMR (DMSO-d_6, δ) : 0.80-5.15 (25H, m); 6.80-8.25 (9H, m); 8.95-9.25 (1H, m); 10.40-10.60 (1H, br s); 11.00 (1H, s)
MASS : 624 (M+1) (free)

4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-[2-(1-pyrrolidino)ethyl]carbamoylmethyl]piperazine dihydrochloride

mp : 183-190°C
$[\alpha]_D^{22}$: -9.4° (C=0.5, DMF)
IR (Nujol) : 3700-3100, 2750-1955, 1683, 1635, 1273, 1170, 1123, 900 cm^{-1}

NMR (DMSO-d_6, δ) : 1.80-5.10 (23H, m); 6.60-8.30 (9H, m); 8.90-9.15 (1H, m); 10.75-10.95 (1H, m); 10.98 (1H, s)
MASS : 610 (M+1) (free), 456

8) (2R)-4-[N-[3-(Diethylamino)propyl]carbamoylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine dihydrochloride

mp : 159-170°C
$[\alpha]_D^{26}$: -6.2° (C=0.5, DMF)
IR (Nujol) : 3650-3100, 2750-1950, 1635, 1276, 1171, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.15-1.30 (8H, m); 3.00-5.15 (19H, m); 6.60-8.30 (9H, m); 8.90-9.15 (1H, m); 10.40-10.70 (1H, m); 11.00-11.10 (1H, m)
MASS : 626 (M+1) (free)

9) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(N,N-dimethylcarbamoylmethyl)piperazine hydrochloride

mp : 165-168°C
$[\alpha]_D^{22}$: -29.0° (C =0.5, MeOH)
IR (Nujol) : 3600-3100, 2700-2100, 1650, 1278, 1174, 1130, 902 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-5.15 (17H, m); 6.80-8.25 (8H, m); 10.10-10.40 (1H, m); 11.01 (1H, s)
MASS : 541 (M+1) (free)

12) (2R)-4-(3-Carbamoylpropyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

mp : 165-170°C
IR (Nujol) : 3670-3050, 2750-2000, 1635, 1275, 1171, 1128, 903 cm^{-1}
NMR (DMSO-d_6, δ) : 1.80-5.20 (15H, m); 6.60-8.30 (10H, m); 10.95 (1H, s); 11.22 (1H, br s)
MASS : 541 (M+1) (free), 457

13) (2R)-4-(Carbamoylmethyl)-1-(3,5-dimethylbenzoyl)-2-(1H-indol-3-yl-methyl)piperazine

mp : >225°C
$[\alpha]_D^{21}$: +41.0° (C=0.5, DMF)
IR (Nujol) : 3410, 3200, 1674, 1610, 1220, 750 cm^{-1}
NMR (DMSO-d_6, δ) : 2.16 (6H, s); 2.50 (2H, s); 2.60-5.00 (9H, m); 6.50-7.85 (10H, m); 10.81 (1H, s)
MASS : 405 (M+1)

14) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-(4-methyl-1-piperazinyl)carbamoylmethyl]piperazine dihydrochloride pentahydrate

mp : 212-216°C
$[\alpha]_D^{29}$: -13.0° (C=0.5, MeOH)
IR (Nujol) : 3650-3100, 2750-2000, 1685, 1632, 1276, 1176, 1131, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.40-5.10 (22H, m); 6.60-8.30 (9H, m); 9.62 (1H, s); 10.20-10.60 (1H, m); 11.01 (1H, s); 11.00-11.30 (1H, m)
MASS : 611 (M+1) (free)

15) (2R)-4-[N-(2-Diethylaminoethyl)carbamoylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl) piperazine dihydrochloride

mp : 176-179°C
$[\alpha]_D^{19}$: -8.4° (C=0.5, DMF)
IR (Nujol) : 3650-3100, 2750-2000, 1681, 1635, 1275, 1173, 1130, 901 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20-1.30 (6H, m); 2.70-5.20 (19H, m); 6.60-8.30 (9H, m); 9.09 (1H, br s); 10.60 (1H, br s); 10.99 (1H, s)
MASS : 612 (M+1) (free)

16) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-(isopropyl)carbamoylmethyl]piperazine

mp : 130-134°C
$[\alpha]_D^{18}$: -12.6° (C=0.5, DMF)
IR (Nujol) : 3500-3100, 1678, 1626, 1277, 1168, 1126, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.09 (6H, d, J=6.5Hz); 2.10-5.00 (12H, m); 6.60-8.20 (9H, m); 10.85 (1H, s)
MASS : 555 (M+1)

17) (2R)-4-[N-(Benzyloxycarbonylmethyl)carbamoylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 90-93°C
$[\alpha]_D^{20}$: -13.6° (C=0.5, MeOH)
IR (Nujol) : 3600-3100, 1739, 1662, 1628, 1510, 1277, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-5.20 (15H, m); 6.60-8.35 (14H, m); 10.84 (1H, s)
MASS : 661 (M+1)

18) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-(2-dimethylaminoethyl)carbamoylmethyl]piperazine

mp : 123-125°C
$[\alpha]_D^{19}$: -12.6° (C=0.5, MeOH)
IR (Nujol) : 3400-3100, 1659, 1630, 1510, 1279, 1126, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.16 (6H, s); 2.30-5.00 (15H, m); 6.60-8.20 (9H, m); 10.86 (1H, s)
MASS : 584 (M+1)

19) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-(3-pyridylmethyl)carbamoylmethyl]piperazine

mp : 105-109°C
$[\alpha]_D^{19}$: -26.5° (C=0.5, MeOH)
IR (Nujol) : 3600-3100, 1628, 1510, 1275, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.10-5.00 (13H, m); 6.60-8.60 (13H, m); 10.84 (1H, s)
MASS : 604 (M+1)

20) (2R)-4-[N-(4-Fluorobenzyl)carbamoylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 94-97°C
$[\alpha]_D^{20}$: -34.4° (C=0.5, MeOH)
IR (Nujol) : 3600-3100, 1628, 1509, 1276, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.15-5.20 (13H, m); 6.60-8.50 (13H, m); 10.84 (1H, s)
MASS : 621 (M+1), 456

21) (2R)-4-[N-(Cyclohexylmethyl)carbamoylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 100-103°C
$[\alpha]_D^{21}$: -17.6° (C=0.5, MeOH)
IR (Nujol) : 3500-3100, 1630, 1522, 1276, 1170, 1130, 898 cm^{-1}
NMR (DMSO-d_6, δ) : 0.80-2.40 (13H, m); 2.60-5.20 (11H, m); 6.60-8.20 (9H, m); 10.86 (1H, s)
MASS : 609 (M+1), 456

22) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-(2-methoxyethyl)carbamoylmethyl]piperazine hydrochloride

$[\alpha]_D^{21}$: -7.2° (C=0.5, DMF)
IR (Nujol) : 3700-3100, 2700-2000, 1720-1590, 1271, 1120, 900 cm^{-1}

NMR (DMSO-d_6, δ) : 2.70-5.10 (18H, m); 6.60-8.90 (9H, m); 10.98 (1H, s)
MASS : 571 (M+1) (free)

23) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[N-(2-hydroxyethyl)carbamoylmethyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

mp : 150-160°C
IR (Nujol) : 3600-3100, 2700-2100, 1670, 1635, 1276, 1173, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.70-5.10 (16H, m); 6.60-8.80 (9H, m); 10.97 (1H, s)
MASS : 557 (M+1) (free), 456

25) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-4-[[4-(2-hydroxyethyl)-1-piperazinyl]carbonylmethyl]-2-(1H-indol-3-yl-methyl)piperazine dihydrochloride

mp : 199-208°C
$[\alpha]_D^{19}$: -25.4° (C=0.5, DMF)
IR (Nujol) : 3650-3050, 2750-2000, 1645, 1275, 1173, 1128, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.90-5.20 (24H, m); 6.60-8.30 (8H, m); 10.30-10.80 (1H, m); 11.00 (1H, s); 11.00-11.35 (1H, br s)
MASS : 626 (M+1) (free)

26) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[[4-(2-pyridyl)-1-piperazinyl]carbonylmethyl]piperazine trihydrochloride

mp : 190-200°C
IR (Nujol) : 3650-3050, 2750-1980, 1635, 1272, 1170, 1122, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 3.00-5.20 (19H, m); 6.20-8.30 (12H, m); 11.02 (1H, s)
MASS : 659 (M+1) (free), 456

27) (2R)-4-[(4-Acetyl-1-piperazinyl)carbonylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl) piperazine hydrochloride

mp : 180-190°C
$[\alpha]_D^{19}$: -31.6° (C=0.5, DMF)
IR (Nujol) : 3650-3100, 2750-2000, 1635, 1278, 1172, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.05 (3H, s); 3.00-5.20 (19H, m); 6.60-8.30 (8H, m); 10.20-10.60 (1H, m); 11.01 (1H, s)
MASS : 624 (M+1) (free)

28) (2R)-1-[3,5-Bis (trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-phenyl-1-piperazinyl)carbonylmethyl] piperazine dihydrochloride

mp : 190-200°C
$[\alpha]_D^{22}$: -30.6° (C=0.5, DMF)
IR (Nujol) : 3650-3100, 2750-2000, 1640, 1279, 1172, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.70-5.30 (19H, m); 6.60-8.30 (13H, m); 10.50-10.70 (1H, m); 11.03 (1H, s)
MASS : 658 (M+1) (free)

29) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4,1'-bipiperidin-1-yl)carbonylmethyl]piperazine dihydrochloride

mp : 209-220°C
$[\alpha]_D^{24}$: -31.6° (C=0.5, DMF)
IR (Nujol) : 3680-3050, 2750-1990, 1640, 1274, 1170, 1127, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20-5.20 (30H, m); 6.60-8.25 (8H, m); 10.20-10.50 (1H, m); 11.02 (2H, br s)
MASS : 664 (M+1) (free)

30) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-cyclohexyl-1-piperazinyl)carbonylmethyl]piperazine dihydrochloride

mp : 207-220°C
$[\alpha]_D^{22}$: -24.0° (C=0.5, DMF)
IR (Nujol) : 3650-3050, 2750-2000, 1650, 1278, 1172, 1131, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.00-5.10 (30H, m); 6.60-8.25 (8H, m); 10.40-10.80 (1H, m); 10.99 (1H, s); 11.62 (1H, br s)
MASS : 664 (M+1) (free), 456

31) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-propyl-1-piperazinyl)carbonylmethyl] piperazine dihydrochloride

mp : 206-214°C
$[\alpha]_D^{22}$: -25.4° (C=0.5, DMF)
IR (Nujol) : 3650-3100, 2750-1980, 1640, 1278, 1173, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 0.92 (3H, t, J=7.2Hz); 1.65-5.20 (23H, m); 6.60-8.25 (8H, m); 10.99 (1H, s); 11.45-11.70 (1H, m)
MASS : 624 (M+1) (free)

32) (2R)-4-[((2S)-2-Carbamoyl-1-pyrrolidino)carbonylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

mp : 196-203°C
$[\alpha]_D^{24}$: -50.6° (C=0.5, DMF)
IR (Nujol) : 3600-3050, 2750-2000, 1650, 1277, 1171, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.80-5.20 (18H, m); 6.60-8.30 (10H, m); 10.20-11.00 (1H, m); 11.02 (1H, s)
MASS : 610 (M+1) (free)

33) (2R)-4-[(4-Acetylamino-4-phenylpiperidino)carbonylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

mp : 210-219°C
$[\alpha]_D^{24}$: -25.0° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 2700-2000, 1645, 1278, 1173, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.60-5.15 (22H, m); 6.60-8.25 (14H, m); 10.00-10.30 (1H, m); 11.01 (1H, s)
MASS : 714 (M+1) (free)

34) (2R)-4-[(4-Ethoxycarbonylpiperidino)carbonylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

$[\alpha]_D^{23}$: -11.4° (C=0.5, DMF)
IR (Neat) : 3260, 1724, 1630, 1276, 1174, 1128, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.18 (3H, t, J=7.1Hz); 1.20-5.00 (22H, m); 6.60-8.20 (8H, m); 10.87 (1H, s)
MASS : 653 (M+1)

35) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-piperidon-1-yl)carbonylmethyl]piperazine hydrochloride

mp : 160-170°C
$[\alpha]_D^{26}$: -28.6° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 2750-2000, 1710, 1650, 1278, 1175, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.30-5.20 (19H, m); 6.60-8.30 (8H, m); 10.20-10.60 (1H, m); 11.02 (1H, s)
MASS : 595 (M+1) (free)

36) (2R)-4-[(3-Carbamoylpiperidino)carbonylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl) piperazine hydrochloride

mp : 189-196°C
IR (Nujol) : 3600-3100, 2750-2000, 1640, 1277, 1170, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20-5.15 (20H, m); 6.60-8.30 (10H, m); 10.00-10.30 (1H, br s); 11.00 (1H, s)
MASS : 624 (M+1) (free)

40) (2R)-4-[(4-Carbamoylpiperidino)carbonylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl) piperazine hydrochloride

mp : 197-208°C
$[\alpha]_D^{20}$: -29.6° (C=0.5, DMF)
IR (Nujol) : 3650-3050, 2750-2000, 1640, 1275, 1173, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20-5.10 (20H, m); 6.60-8.25 (10H, m); 9.80-10.20 (1H, m); 10.97 (1H, s)
MASS : 624 (M+1) (free)

41) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-methyl-1-homopiperazinyl)carbonyl-methyl]piperazine dihydrochloride

mp : 220-225°C (dec.)
$[\alpha]_D^{21}$: -24.8° (C=0.5, DMF)
IR (Nujol) : 3700-3100, 2750-1980, 1640, 1275, 1172, 1126, 903 cm^{-1}
NMR (DMSO-d_6, δ) : 0.75-1.30 (2H, m); 2.00-5.20 (22H, m); 6.60-8.30 (8H, m); 10.50 (1H, br s); 11.01 (1H, s); 11.45 (1H, br s)
MASS : 610 (M+1) (free)

42) (2R)-4-[(4-Ethyl-1-piperazinyl)carbonylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl) piperazine dihydrochloride

mp : 205-211°C
$[\alpha]_D^{19}$: -27.6° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 2700-2000, 1650, 1276, 1172, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.29 (3H, t, J=7.2Hz); 2.80-5.20 (21H, m); 6.60-8.30 (8H, m); 11.00 (1H, s); 11.60-11.80 (1H, m)
MASS : 610 (M+1) (free)

43) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(piperidinocarbonylmethyl)piperazine hydrochloride

mp : 180-190°C
$[\alpha]_D^{19}$: -26.8° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 2700-2100, 1647, 1278, 1173, 1131, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.40-1.70 (6H, m); 3.10-5.20 (15H, m); 6.60-8.30 (8H, m); 10.00-10.40 (1H, m); 11.00 (1H, s)
MASS : 581 (M+1) (free)

44) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-phenylpiperidino)carbonylmethyl]piperazine hydrochloride

mp : 167-173°C
$[\alpha]_D^{19}$: -30.8° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 2700-2000, 1640, 1276, 1172, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20-5.20 (20H, m); 6.60-8.30 (13H, m); 10.00-10.40 (1H, m); 11.00 (1H, s)
MASS : 657 (M+1) (free)

45) (2R)-4-[(4-Benzylpiperidino)carbonylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

mp : 158-160°C
$[\alpha]_D^{19}$: -27.2° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 2700-2000, 1640, 1276, 1174, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.00-5.20 (22H, m); 6.60-8.30 (13H, m); 9.90-10.40 (1H, m); 10.99 (1H, s)
MASS : 671 (M+1) (free)

46) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(pyrrolidinocarbonylmethyl)piperazine hy-

drochloride

mp : 161-166°C
IR (Nujol) : 3700-3100, 2700-2000, 1640, 1278, 1131, 902 cm^{-1}
NMR (DMSO-d_6, δ) : 1.80-2.00 (4H, m); 3.00-5.20 (15H, m); 6.60-8.30 (8H, m); 11.00 (1H, s)
MASS : 567 (M+1) (free)

47) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-methyl-1-piperazinyl)carbonylmethyl] piperazine

mp : 105-108°C
$[\alpha]_D^{18}$: -12.2° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 1630, 1275, 1165, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.10-5.00 (22H, m); 6.60-8.20 (8H, m); 10.87 (1H, s)
MASS : 596 (M+1)

48) (2R)-4-(4-Carbamoylbenzyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 120-126°C
$[\alpha]_D^{21}$: -37.6° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 1660, 1610, 1276, 1170, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.00-5.00 (11H, m); 6.50-8.30 (14H, m); 10.80 (1H, s)
MASS : 589 (M+1)

49) (2R)-4-[N-(Carbamoylmethyl)carbamoylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl) piperazine

mp : 135-145°C
$[\alpha]_D^{21}$: -15.0° (C=0.5, MeOH)
IR (Nujol) : 3600-3100, 1730-1560, 1277, 1170, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.80-5.00 (13H, m); 6.60-8.20 (11H, m)
MASS : 570 (M+1), 456

50) (2R)-4-(4-Carbamoylbutyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

mp : 146-156°C
$[\alpha]_D^{21}$: +0.4° (C=0.5, DMF)
IR (Nujol) : 3650-3050, 2750-1900, 1635, 1275, 1175, 1125, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.40-5.20 (17H, m); 6.60-8.30 (10H, m); 10.95 (1H, s); 11.05-11.40 (1H, m)
MASS : 555 (M+1) (free)

51) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[3-[(4-methyl-1-homopiperazinyl)carbonyl] propyl]piperazine

$[\alpha]_D^{20}$: -13.5° (C=1.0, MeOH)
IR (Neat) : 3225, 1630, 1430, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 1.63-4.95 (28H, m); 6.60-8.19 (8H, m); 10.89 (1H, s)
MASS : 638 (M+1)

52) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[3-[N-(4-methyl-1-piperazinyl)carbamoyl] propyl]piperazine

$[\alpha]_D^{19}$: -14.1° (C=1.0, MeOH)
IR (Neat) : 3225, 1630, 1450, 1350, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 1.68-4.85 (23H, m); 2.15 (3H, s); 6.64-8.76 (9H, m); 10.85 (1H, s)
MASS : 639 (M+1)

Example 33

[0172] The following compounds were obtained according to a similar manner to that of Preparation Example 10.

1) (2R)-4-(4-Carboxybutyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

mp : 97-100°C
IR (Nujol) : 3600-3100, 2700-2000, 1710, 1625, 1276, 1170, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.35-5.00 (17H, m); 6.60-8.20 (8H, m); 10.85 (1H, s); 12.01 (1H, s)
MASS : 556 (M+1) (free)

3) (2R)-4-[(4-Carboxypiperidino)carbonylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

mp : 143-150°C
IR (Nujol) : 3600-3100, 2750-2000, 1710, 1630, 1277, 1170, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.30-5.00 (20H, m); 6.60-8.20 (8H, m); 10.89 (1H, s); 12.32 (1H, s)
MASS : 625 (M+1) (free)

Example 34

[0173] A mixture of (2R)-4-[3-(benzyloxycarbonyl)propyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.15 g), 10% Pd charcoal (15 mg) and methanol (4.5 ml) was stirred for 3 hours under hydrogen atmosphere (1 atm). The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by column chromatography on a silica gel using chloroform-methanol (5:1) as eluent to give (2R)-4-(3-carboxypropyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.067 g) as a powder.

mp : 112-120°C
$[\alpha]_D^{17}$: +3.6° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 1700, 1625, 1276, 1175, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.60-5.00 (15H, m); 6.60-8.20 (8H, m); 10.85 (1H, s)
MASS : 542 (M+1)

Example 35

[0174] The following compounds were obtained according to a similar manner to that of Example 34.

1) (2R)-4-(Carboxymethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 152-156°C
$[\alpha]_D^{19}$: -3.0° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 1654, 1630, 1277, 1196, 1130 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-5.20 (11H, m); 6.60-8.20 (8H, m); 10.85 (1H, s)
MASS : 514 (M+1)

2) (2R)-4-(Carboxymethyl)-2-(1H-indol-3-yl-methyl)-1-(3,5-dimethylbenzoyl)piperazine

mp : 153-157°C
$[\alpha]_D^{21}$: +47.0° (C=0.5, DMF)
IR (Nujol) : 3600-3150, 1632, 734 cm^{-1}
NMR (DMSO-d_6, δ) : 2.05-5.00 (17H, m); 6.50-7.80 (8H, m); 10.83 (1H, s)
MASS : 406 (M+1)

4) (2R)-4-[N-(Carboxymethyl)carbamoylmethyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

mp : 172-175°C
IR (Nujol) : 3700-3100, 1700-1550, 1277, 1171, 1131, 900 cm^{-1}

NMR (DMSO-d_6, δ) : 2.60-5.00 (13H, m); 6.60-8.20 (9H, m); 10.87 (1H, s)
MASS : 571 (M+1), 456

Example 37

[0175] The following compounds were obtained according to a similar manner to that of Example 23.

3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[4-(dimethylamino)benzoyl]piperazine hydrochloride

IR (Nujol) : 3350-3220, 2600-2550, 2430-2340, 1622 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-5.06 (9H, m); 4.68 (6H, s); 6.50-8.30 (13H, m); 10.85 (1H, s)
MASS : 603 (M+1) (free)

4) (2R)-4-(4-Aminobenzoyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

IR (Nujol) : 3260, 2570, 1600-1590 cm^{-1}
NMR (DMSO-d_6, δ) : 2.66-3.64 (6H, m); 3.82-5.00 (3H, m); 6.50-8.26 (14H, m); 10.88 (1H, s)
MASS : 575 (M+1) (free)

5) (2R)-4-(Carbamoylmethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

mp : >230°C
$[\alpha]_D^{21}$: -21.2° (C=0.5, MeOH)
IR (Nujol) : 3345, 3140, 2800-2400, 1679, 1655, 1276, 1130, 908 cm^{-1}
NMR (DMSO-d_6, δ) : 3.00-5.20 (11H, m); 6.60-8.30 (10H, m); 10.99 (1H, s)
MASS : 513 (M+1) (free), 456

Preparation Example 38 (not within the scope of the invention)

[0176] To a stirred mixture of (2R)-4-(3-aminopropyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)piperazine dihydrochloride (160 mg), nicotinic acid (33 mg) and triethylamine (0.17 ml) in dichloromethane (2 ml) was added 2-chloro-1-methylpyridinium iodide (78 mg) at room temperature. After stirring for 1.5 hours, the reaction mixture was evaporated under reduced pressure. The residue was partitioned between ethyl acetate (30 ml). and water (10 ml). The organic layer was separated and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on a silica gel with dichloromethane-methanol (40:1) as eluent to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[3-(nicotinoylamino)propyl]piperazine (70 mg).

$[\alpha]_D^{20}$: -21.5° (C=1.0, MeOH)
IR (Neat) : 3350, 3000-2700, 1630, 1530, 1430, 1380 cm^{-1}
NMR ($CDCl_3$, δ) : 1.7-2.0 (2H, m); 2.18 and 2.21 (6H, 2 s); 2.4-2.6 (2H, m); 2.6-5.2 (11H, m); 6.5-7.5 (7H, m); 7.82 (1H, br s); 8.12 (1H, d, J=8.0Hz); 8.71 (1H, d, J=3.7Hz); 8.97 (1H, br s)
MASS : 607 (M+1), 544, 502, 445

Example 39

[0177] The following compounds were obtained according to a similar manner to that of Preparation Example 38.

6) (2R)-4-[4-(Acetylamino)benzoyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

IR (Nujol) : 3250, 1628, 1525 cm^{-1}
NMR (DMSO-d_6, δ) : 2.08 (3H, s); 2.90-5.02 (9H, m); 6.54-8.40 (12H, m); 10.14 (1H, s); 10.83 (1H, s)
MASS : 617 (M+1)

7) (2R)-4-[3-(Acetylamino)propyl]-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine hydrochloride

IR (Nujol) : 3210, 1630, 1544 cm^{-1}

NMR (DMSO-d_6, δ) : 1.81 and 1.84 (3H, 2 s); 1.60-2.05 (2H, m); 2.94-5.18 (13H, m); 6.57-8.29 (9H, m); 10.97 (1H, s); 11.28 and 11.36 (1H, 2 br s)
MASS : 555 (M+1) (free)

Preparation Example 40 (not within the scope of the invention)

[0178] To a stirred mixture of (2R)-4-(2-aminoethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)piperazine dihydrochloride (110 mg), triethylamine (0.2 ml) in dichloromethane (10 ml) was added methanesulfonyl chloride (0.1 ml) at 0°C. After stirring for 1 hour, the reaction mixture was poured into ice-water and extracted with ethyl acetate. The extract was washed successively with aqueous saturated sodium bicarbonate solution and brine,- and dried. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on a silica gel eluting with a mixture of dichloromethane and methanol (40:1) and treated with 4N hydrogen chloride in ethyl acetate solution to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(3,4-dimethylbenzyl)-4-[2-(mesylamino)ethyl]piperazine hydrochloride (50 mg).

mp : >220°C
$[\alpha]_D^{22}$: +0.2° (C=0.5, DMF)
IR (Nujol) : 3350, 2700-2400, 1645, 1500, 1450, 1380 cm^{-1}
NMR (DMSO-d_6, δ) : 2.10 and 2.18 (6H, 2 s); 2.7-5.2 (17H, m); 6.6-7.7 (5H, m); 8.1-8.2 (1H, m); 11.05-11.4 (1H, m)
MASS : 566 (M+1) (free)

Example 41

[0179] The following compounds were obtained according to a similar manner to that of Preparation Example 40.

3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[4-(mesylamino)benzoyl]piperazine

IR (Nujol) : 3260-3170, 1627 cm^{-1}
NMR (DMSO-d_6, δ) : 3.06 (3H, s); 2.60-3.66 (6H, m); 3.84-5.02 (3H, m); 6.52-8.44 (12H, m); 10.05 (1H, s); 10.83 (1H, s)
MASS : 653 (M+1)

4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(phenylsulfonyl)piperazine

$[\alpha]_D^{21}$: +46.1° (C=1.0, MeOH)
IR (Neat) : 3500-3100, 1635, 1276, 1165, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-5.00 (9H, m); 6.40-8.20 (13H, m); 10.90 (1H, br s)
MASS : 596 (M+1)

Example 42

[0180] A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(phthalimidomethylcarbonyl) piperazine (250 mg), hydrazine hydrate (50 mg) in ethanol (5 ml) was heated under reflux for 2 hours. The resulting precipitate was removed by filtration and the filtrate was evaporated under reduced pressure. The residue was washed with aqueous 1N sodium hydroxide solution and then purified by column chromatography on a silica gel eluting with a mixture of ethyl acetate and methanol (4:1) to afford (2R)-4-(2-aminoacetyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (110 mg).

mp : 110-120°C
$[\alpha]_D^{21}$: -4.4° (C=1.0, MeOH)
IR (Nujol) : 3600-3100, 1634, 1277, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-5.20 (13H, m); 6.55-8.30 (8H, m); 10.87 (1H, br s)
MASS : 513 (M+1), 456

Preparation Example 44 (not in the scope of the invention)

[0181] A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(4-nitrobenzyl)piperazine (360 mg), iron powder (360 mg), ammonium chloride (36 mg) and water (1.5 ml) in ethanol (6 ml) was heated under

reflux for 40 minutes. After cooling, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on a silica gel eluting with a mixture of dichloromethane and methanol (10:1) to give (2R)-4-(4-aminobenzyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.34 g).

$[\alpha]_D^{18}$: -35.8° (C=0.5, DMF)
IR (Neat) : 3500-3100, 1623, 1514, 1274, 1170, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 1.90-4.90 (11H, m); 4.97 (2H, s); 6.50-8.20 (12H, m); 10.80 (1H, s)
MASS : 561 (M+1), 456

Example 45

[0182] The following compound was obtained according to a similar manner to that of Preparation Example 44.

[0183] (2R)-4-(4-Aminobenzoyl)-1-[3,5-bis(trifluoromethyl)-benzoyl]-2-(1H-indol-3-yl-methyl)piperazine

IR (Neat) : 3330, 3000, 2910, 1625-1600, 1515 cm^{-1}
NMR (DMSO-d_6, δ) : 2.60-3.64 (5H, m); 3.80-4.40 (4H, m); 4.79-5.70 (2H, m); 6.43-8.40 (12H, m); 10.85 (1H, s)
MASS : 575 (M+1)

Example 46

[0184] A solution of 4N hydrogen chloride in ethyl acetate solution (1.5 ml) was added dropwise to a solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-trityl-1-piperazinyl)carbonylmethyl]piperazine (480 mg) in ethyl acetate (5 ml) at 0°C. The resulting mixture was stirred at the same temperature for 1 hour and then allowed to stand overnight. Aqueous saturated sodium bicarbonate solution (20 ml) was added to the reaction mixture, and the product was extracted with ethyl acetate. The organic phase was washed with brine and dried. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on a silica gel eluting with a mixture of dichloromethane and methanol (5:1) and treated with 4N hydrogen chloride in dioxane solution to afford (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(1-piperazinyl)carbonylmethyl]piperazine dihydrochloride (250 mg).

mp : 210-218°C
$[\alpha]_D^{19}$: -25.6° (C=0.5, DMF)
IR (Nujol) : 3650-3100, 2700-2000, 1645, 1275, 1174, 1130, 902 cm^{-1}
NMR (DMSO-d_6, δ) : 3.00-5.20 (20H, m); 6.60-8.30 (8H, m); 9.73 (2H, br s); 10.99 (1H, s)
MASS : 582 (M+1) (free)

Example 47

[0185] A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(2-chloroacetyl)-2-(1H-indol-3-yl-methyl)piperazine (730 mg), potassium phthalimide (260 mg) in dimethylformamide (10 ml) was stirred at room temperature for 7 hours and then poured into aqueous sodium chloride solution (100 ml). The resulting precipitate was collected by filtration, washed with water and dried. The crude product was dissolved in toluene (7 ml) and filtered. To the filtrate was added n-hexane (35 ml) and the whole was stirred for 10 minutes. The resulting powder was collected by filtration, washed with ethyl ether and dried to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(phthalimidomethylcarbonyl)piperazine (500 mg).

mp : >220°C
$[\alpha]_D^{19}$: -1.2° (C=0.5, DMF)
IR (Nujol) : 3500-3200, 1772, 1708, 1647, 1275, 1183, 1131, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.50-5.20 (11H, m); 6.60-8.30 (12H, m); 10.83-10.94 (1H, m)
MASS : 643 (M+1)

Example 48

[0186] A mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (150 mg), acrylamide (24 mg) in toluene (1.5 ml) was stirred at room temperature for 1 hour and then was refluxed for 5 hours. After additional acrylamide (24 mg) was added, the whole mixture was refluxed for 3 hours and evaporated under reduced pressure.

The obtained residue was purified by column chromatography on a silica gel eluting with a mixture of ethyl acetate and methanol (10:1) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(2-carbamoylethyl)-2-(1H-indol-3-yl-methyl)piperazine (89 mg).

mp : 80-100°C
$[\alpha]_D^{17}$: +3.6° (C=0.5, DMF)
IR (Nujol) : 3600-3100, 1673, 1636, 1276, 1170, 1130, 900 cm^{-1}
NMR (DMSO-d_6, δ) : 2.00-4.90 (13H, m); 6.60-8.20 (10H, m); 10.84 (1H, s)
MASS : 527 (M+1), 456

Example 50

[0187] The following piperazine derivatives (Table 1) were prepared by the similar manner to that of the each Example No. defined in the "Process" column. The physical properties of the object compounds are shown after the table.

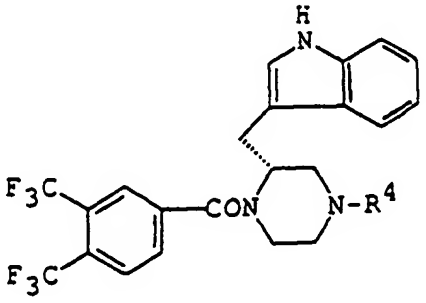


Table 1

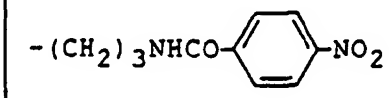
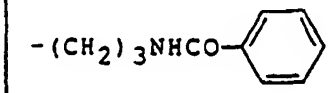
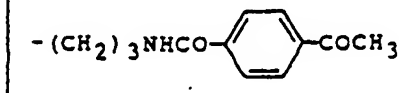
Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
50-1)	$-(CH_2)_4NHSO_2CH_3$	HCl	Ex.50-21)	Prep. Ex. 40
50-2)		HCl	Ex.50-20)	Prep. Ex. 40
50-3)	$-(CH_2)_3NHCOOC_2H_5$	HCl	Ex.50-20)	Prep. Ex. 40
50-4)		HCl	Ex.50-20)	Prep. Ex. 40
50-5)	$-(CH_2)_3NHCOCOOC_2H_5$	HCl	Ex.50-20)	Prep. Ex. 40
50-6)		HCl	Ex.50-20)	Prep. Ex. 40
50-7)	$-(CH_2)_3NHSO_2CH_3$	HCl	Ex.50-20)	Prep. Ex. 40
50-8)		HCl	Ex.50-20)	Prep. Ex. 38

Table 1 (continued)

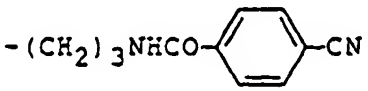
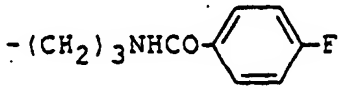
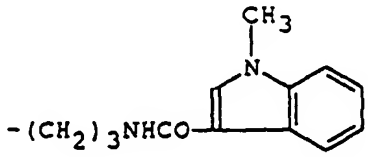
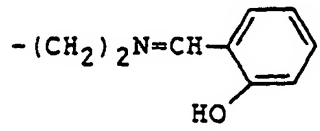
Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
50-9)		HCl	Ex.50-20)	Prep. Ex. 38
50-10)		HCl	Ex.50-20)	Prep. Ex. 38
50-11)		HCl	Ex.50-20)	Prep. Ex. 38
50-12)	$-(CH_2)_2NHSO_2CH_3$	HCl	Ex. 65	Prep. Ex. 40
50-13)		-	Ex. 6	Prep. Ex. 14
50-14)	$-CH_2CN$	-	Ex. 6	Ex. 11

Table 1 (continued)

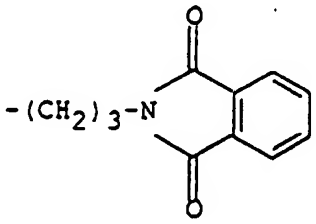
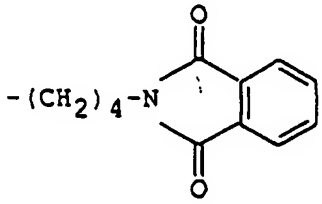
Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
50-15)	$-(CH_2)_3CN$	-	Ex. 6	Ex. 11
50-16)		-	Ex. 6	Ex. 11
50-17)		-	Ex. 6	Ex. 11
50-18)	$-CH_2CN$	HCl	Ex.50-14)	Ex. 23
50-19)	$-(CH_2)_3CN$	HCl	Ex.50-15)	Ex. 23
50-20)	$-(CH_2)_3NH_2$	2HCl	Ex.50-16)	Ex. 42

Table 1 (continued)

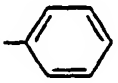
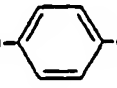
Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
50-21)	$-(CH_2)_4NH_2$	2HCl	Ex.50-17)	Ex. 42
50-22)	$-(CH_2)_3NHCONH-$ 	HCl	Ex.50-20)	Ex. 62
50-23)	$-CO-$  $-COOCH_3$	-	Ex.6	Prep. Ex. 16
50-24)	$-CO-$  $-COOH$	-	Ex.50-23)	Prep. Ex. 10
50-26)	$-CON(CH_3)-(CH_2)_3CH_3$	-	Ex. 6	Ex. 63
50-27)	$-CH_2CON(CH_3)(OCH_3)$	-	Ex.35-1)	Prep. Ex. 27

Table 1 (continued)

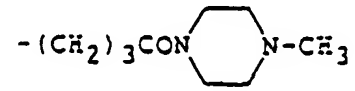
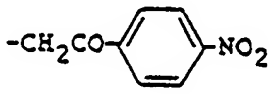
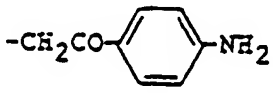
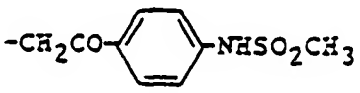
Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
50-28)	$-(CH_2)_3CONHOCH_3$	ECl	Ex. 34	Prep. Ex. 27
50-29)		-	Ex. 34	Prep. Ex. 27
50-30)	$-(CH_2)_3CONHCH_3$	-	Ex. 34	Prep. Ex. 27
50-31)	$-CH_2CONHOCH_3$	-	Ex.35-1)	Prep. Ex. 27
50-32)		-	Ex. 6	Ex. 11
50-33)		-	Ex.50-32)	Ex. 44
50-34)		-	Ex.50-33)	Prep. Ex. 40

Table 1 (continued)

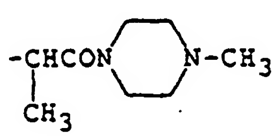
Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
50-35)	$-CO(CH_2)_3N(CH_3)_2$	HCl	Ex. 61	Ex. 23
50-36)	$-CH(CH_3)COOC_2H_5$	-	Ex. 6	Ex. 11
50-37)	$-CH(CH_3)COOH$	-	Ex.50-36) Prep.	Prep. Ex. 10
50-38)	$-CH(CH_3)CONHOCH_3$	-	Ex.50-37)	Prep. Ex. 27
50-39)	$-CH(CH_3)CONH_2$	-	Ex.50-37)	Prep. Ex. 27
50-40)		HCl	Ex.50-37)	Prep. Ex. 27

Table 1 (continued)

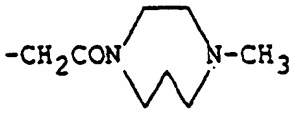
Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
50-42)		citric acid	Ex.32-41)	Ex. 23

Table 1 (continued)

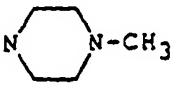
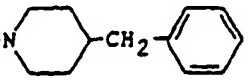
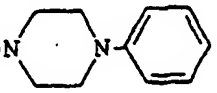
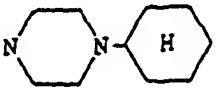
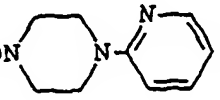
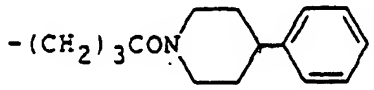
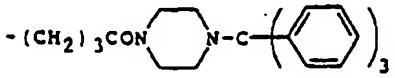
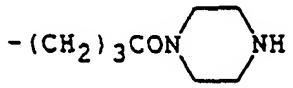
Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
50-48)	$-(CH_2)_3-CONHN$ 	H_2SO_4	Ex.32-52)	Ex. 23
50-49)	$-(CH_2)_3CON$ 	HCl	Ex. 34	Ex. 72
50-50)	$-(CH_2)_3CON$ 	2HCl	Ex. 34	Ex. 72
50-51)	$-(CH_2)_3CON$ 	2HCl	Ex. 34	Ex. 72
50-52)	$-(CH_2)_3CONH(CH_2)_2N(CH_3)_2$	2HCl	Ex. 34	Ex. 72
50-53)	$-(CH_2)_3CON$ 	HCl	Ex. 34	Ex. 72
50-54)	$-(CH_2)_3CON$ 	3HCl	Ex. 34	Ex. 72

Table 1 (continued)

Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
50-55)		HCl	Ex. 34	Ex. 72
50-56)		-	Ex. 34	Ex. 72
50-57)		2HCl	Ex.50-56)	Ex. 46
50-58)		H_2SO_4	Ex. 34	Ex. 72

[0188] Physical properties of the compounds of the Example 50 :

Example 50-1)

[0189]

IR (Nujol) : 3260-3170, 1635 cm^{-1}
NMR(DMSO-d_6, δ) : 1.40-1.94 (4H, m); 2.80-5.20 (13H, m); 2.90, 2.92 (3H, 2 s); 6.60-8.30 (9H, m); 10.95 (1H, s); 10.86-11.32 (1H, m)
MASS : 605 (M+1) (free)

Example 50-2)

[0190]

IR (Nujol) : 3230, 2570, 1638, 1596 cm^{-1}
NMR (DMSO-d_6, δ) : 1.90-2.20 (2H, m); 3.00-5.20 (13H, m); 6.59-8.40 (12H, m); 8.98-9.13 (1H, m); 10.96 (1H, s); 10.95-11.34 (1H, m)
MASS : 662 (M+1) (free)

Example 50-3)

[0191]

IR (Nujol) : 3260, 2560, 1697, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 1.07-1.23 (3H, m); 1.70-2.05 (2H, m); 2.95-5.18 (15H, m); 6.60-8.30 (9H, m); 10.96 (1H, s); 11.00-11.38 (1H, m)
MASS : 585 (M+1) (free)

Example 50-4)

[0192]

IR (Nujol) : 3230, 2560, 1635, 1574, 1531 cm^{-1}
NMR (DMSO-d_6, δ) : 1.82-2.18 (2H, m); 2.94-5.24 (13H, m); 6.57-8.29 (13H, m); 8.63-8.80 (1H, m); 10.96 (1H, s); 10.86-11.27 (1H, m)
MASS : 617 (M+1) (free)

Example 50-5)

[0193]

IR (Nujol) : 3240, 2560, 1734, 1685, 1635, 1523 cm^{-1}
NMR (DMSO-d_6, δ) : 1.28 (3H, t, J=7.06Hz); 1.75-2.14 (2H, m); 2.88-4.16, 4.49-4.67, 5.02-5.21 (13H, m); 4.24 (2H, q, t=7.06Hz); 6.57-8.29 (8H, m); 9.11 (1H, m); 10.96 (1H, s); 11.03-11.35 (1H, m)
MASS : 613 (M+1) (free)

Example 50-6)

[0194]

IR (Nujol) : 3350-3200, 1636 cm^{-1}
NMR (DMSO-d_6, δ) : 1.89-2.08 (2H, m); 2.70-2.94 (2H, m); 2.94-4.15, 4.50-4.68, 5.00-5.20 (11H, m); 6.57-8.31 (14H, m); 10.96 (1H, s); 11.05-11.40 (1H, m)
MASS : 653 (M+1) (free)

Example 50-7)

[0195]

IR (Nujol) : 3150, 1601 cm^{-1}
NMR (DMSO-d_6, δ) : 1.82-2.14 (2H, m); 2.92, 2.94 (3H, s); 2.96-4.17, 4.50-4.70, 5.04-5.20 (13H, m); 6.60-8.28 (9H, m); 10.94 (1H, s); 11.25, 11.40 (1H, br s)
MASS : 591 (M+1) (free)

Example 50-8)

[0196]

IR (Nujol) : 3240, 1677, 1635, 1538 cm^{-1}
NMR (DMSO-d_6, δ) : 1.85-2.20 (2H, m); 2.62 (3H, s); 3.00-4.23, 4.49-4.67, 5.05-5.21 (13H, m); 6.12-8.27 (12H), m); 8.91 (1H, m); 10.94 (1H, s); 11.04-11.37 (1H, m)
MASS : 659 (M+1) (free)

Example 50-9)

[0197]

IR (Nujol) : 3250, 1638 cm^{-1}
NMR (DMSO-d_6, δ) : 1.82-2.24 (2H, m); 2.90-5.20 (13H, m); 6.55-8.28 (12H, m); 8.90-9.10 (1H, m); 10.96 (1H, s); 10.84-11.34 (1H, m)
MASS : 642 (M+1) (free)

Example 50-10)

[0198]

IR (Nujol) : 3230, 1634 cm^{-1}
NMR (DMSO-d_6, δ) : 1.87-2.20 (2H, m); 2.94-5.24 (13H, m); 6.56-8.29 (12H, m); 8.66-8.88 (1H, m); 10.96 (1H, s); 10.90-11.33 (1H, m)
MASS : 635 (M+1) (free)

Example 50-11)

[0199]

IR (Nujol) : 3240, 2710-2570, 1630, 1540 cm^{-1}
NMR (DMSO-d_6, δ) : 1.89-2.20 (2H, m); 3.00-5.20 (13H, m); 3.83 (3H, s); 6.59-8.26 (14H, m); 10.95 (1H, s); 10.84-11.28 (1H, m)
MASS : 670 (M+1) (free)

Example 50-12)

[0200]

IR (Nujol) : 3250, 1634 cm^{-1}
NMR (DMSO-d_6, δ): 2.98, 3.01 (3H, 2 s); 2.60-5.18 (13H, m); 6.54-8.25 (9H, m); 10.95 (1H, s); 11.12-11.52 (1H, m)
MASS : 577 (M+1) (free)

Example 50-13)

[0201]

IR (Neat) : 3240, 3040, 2910, 1653-1612 cm^{-1}
NMR ($CDCl_3$, δ) : 2.20-4.10 (13H, m); 6.77-8.44 (15H, m)
MASS : 603 (M+1)

Example 50-14)

[0202]

IR ($CHCl_3$) : 3270, 2990, 2920, 2220, 1714, 1661-1610 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-3.45, 3.70-4.00, 4.26-4.44, 4.85-5.05 (11H, m); 6.55-8.24 (8H, m); 10.87 (1H, s)
MASS : 495 (M+1)

Example 50-15)

[0203]

IR (Neat) : 3280, 2230, 1664, 1626 cm^{-1}
NMR (DMSO-d_6, δ) : 1.64-2.44 (4H, m); 2.54-4.97 (11H, m); 6.56-8.25 (8H, m); 10.86 (1H, s)
MASS : 523 (M+1)

Example 50-16)

[0204]

IR (Neat) : 3270, 2920, 1766, 1703, 1667, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.70-2.45 (4H, m); 2.78-4.92 (11H, m); 6.54-8.22 (12H, m); 10.83 (1H, s)
MASS : 643 (M+1)

Example 50-17)

[0205]

IR ($CHCl_3$) : 3300, 2920, 1766, 1706, 1627 cm^{-1}
NMR (DMSO-d_6, δ) : 1.35-1.82 (4H, m); 1.85-2.44 (2H, m); 2.70-4.35, 4.76-4.94 (11H, m); 6.56-8.22 (12H, m); 10.84 (1H, s)
MASS : 657 (M+1)

Example 50-18)

[0206]

IR (Neat) : 3280, 2910, 2210, 1740, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-5.06 (11H, m); 6.54-8.24 (8H, m); 10.89 (1H, s); 10.75-11.03 (1H, m)
MASS : 495 (M+1) (free)

Example 50-19)

[0207]

IR (Nujol) : 3360-3230, 2710-2230, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 2.00-2.27 (2H, m); 2.58-2.80 (2H, m); 2.96-5.19 (11H, m); 6.56-8.28 (8H, m); 10.94 (1H, s); 11.36-11.73 (1H, m)
MASS : 523 (M+1) (free)

Example 50-20)

[0208]

IR (Nujol) : 3450, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 1.96-2.28 (2H, m); 2.75-5.22 (13H, m); 6.56-8.30 (11H, m); 10.96 (1H, s); 11.54-11.88 (1H, m)
MASS : 513 (M+1) (free)

Example 50-21)

[0209]

IR (Nujol) : 3340, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 1.50-2.00 (4H, m); 2.68-5.20 (13H, m); 6.56-8.28 (11H, m); 10.96 (1H, s); 11.54 (1H, br s)
MASS : 527 (M+1) (free)

Example 50-22)

[0210]

IR (Nujol) : 3270, 1637, 1595 cm^{-1}
NMR (DMSO-d_6, δ) : 1.68-2.10 (2H, m); 3.00-3.74, 4.02-4.19, 4.49-4.68, 5.05-5.20 (13H, m); 6.43-8.28 (14H, m); 8.75, 8.81 (1H, s); 10.95 (1H, s); 10.72-11.00 (1H, m)
MASS : 632 (M+1) (free)

Example 50-23)

[0211]

IR (Neat) : 3250, 2980, 2900, 1714, 1625, 1575 cm^{-1}
NMR (DMSO-d_6, δ) : 2.87-5.03 (9H, m); 3.89 (3H, s); 6.45-8.26 (12H, m); 10.78, 10.89 (1H, 2 br s)
MASS : 618 (M+1)

Example 50-24)

[0212]

IR (Neat) : 3330-3220, 2960, 1612, 1540 cm^{-1}
NMR (DMSO-d_6, δ) : 2.83-4.43 (10H, m); 6.54-8.22 (12H, m); 10.88 (1H, s)
MASS : 604 (M+1)

Example 50-26)

[0213]

IR (Neat) : 3260, 2920, 2850, 1626 cm^{-1}
NMR (DMSO-d_6, δ) : 0.88 (3H, t, J=7.2Hz); 1.10-1.63 (4H, m); 2.85 (3H, s); 2.69-5.05 (11H, m); 6.57-8.30 (8H, m); 10.88 (1H, s)
MASS : 569 (M+1)

Example 50-27)

[0214]

$[\alpha]_D^{21}$: -4.6° (C=1.0, MeOH)
IR (Neat) : 3300, 1630, 1430, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 2.20-4.90 (11H, m); 3.13 (3H; s); 3.71 (3H, s); 6.60-8.20 (8H, m); 10.86 (1H, s)
MASS : 557 (M+1)

Example 50-28)

[0215]

$[\alpha]_D^{21}$: -7.0° (C=1.0, MeOH)
IR (Neat) : 3150, 2550, 2440, 2325, 1640, 1430, 1355, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 2.0-5.20 (15H, m); 3.60 (3H, s); 6.17-8.23 (8H, m); 10.97 (1H, s); 11.3 (1H, br s)
MASS : 571 (M+1) (free)

Example 50-29)

[0216]

$[\alpha]_D^{20}$: -14.7° (C=1.0, MeOH)
IR (Neat) : 3260, 1625, 1430, 1350, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 1.60-4.95 (23H, m); 2.16 (3H, s); 6.6-8.19 (8H, m); 10.87 (1H, s)
MASS : 624 (M+1)

Example 50-30)

[0217]

$[\alpha]_D^{20}$: -10.5° (C=1.0, MeOH)
IR (Neat) : 3260, 1650, 1630, 1570, 1430, 1350, 1275 cm^{-1}

NMR (DMSO-d_6, δ) : 1.63-4.90 (15H, m); 2.59 (2H, d); 6.15-8.20 (9H, m); 10.87 (1H, s)
MASS : 555 (M+1)

Example 50-31)

[0218]

$[\alpha]_D^{20}$: -6.2° (C=1.0, MeOH)
IR (Neat) : 3250, 1670, 1625, 1430, 1350, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 2.0-4.85 (9H, m); 2.97 (2H, s); 3.63 (3H, s); 6.63-8.18 (8H, m); 10.86 (1H, s); 11.15 (1H, s)
MASS : 543 (M+1)

Example 50-32)

[0219]

$[\alpha]_D^{21}$: -18.9° (C=1.0, MeOH)
IR (Neat) : 3300, 1690, 1625, 1525, 1430, 1345, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 2.2-4.93 (11H, m); 6.54-8.48 (13H, m); 10.83 (1H, s)
MASS : 619 (M+1)

Example 50-33)

[0220]

$[\alpha]_D^{21}$: -34.8° (C=1.0, MeOH)
IR (Neat) : 3350, 1620, 1590, 1440, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 2.1-4.96 (11H, m); 5.94-8.26 (13H, m); 10.82 (1H, s)
MASS : 589 (M+1)

Example 50-34)

[0221]

$[\alpha]_D^{30}$: -18.9° (C=1.0, MeOH)
IR (Neat) : 3400, 1685, 1625, 1365, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 1.99 (3H, s); 2.10-4.93 (11H, m); 6.53-8.28 (12H, m); 10.81 (1H, s)
MASS : 667 (M+1)

Example 50-35)

[0222]

IR (Nujol) : 3350-3200, 2710, 1624 cm^{1}
NMR (DMSO-d_6, δ) : 1.77-2.10 (2H, m); 2.28-5.18 (13H, m); 2.74, 2.76 (6H, 2 s); 6.55-8.24 (8H, m); 10.51 (1H, br s); 10.93 (1H, s)
MASS : 569 (M+1) (free)

Example 50-36)

[0223]

IR (Neat) : 3300, 1720, 1630, 1430, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 1.1-1.32 (6H, m); 2.2-4.93 (13H, m); 6.57-8.21 (8H, m); 10.84 (1H, s)
MASS : 556 (M+1)

Example 50-37)

[0224]

$[\alpha]_D^{20}$: -23.3° (C=1.0, MeOH)
IR (Neat) : 3300, 1730, 1640, 1460, 1375, 1280 cm^{-1}
NMR (DMSO-d_6, δ) : 1.4-1.6 (3H, m); 2.8-5.1 (10H, m); 6.6-8.26 (8H, m); 10.93 (1H, s)
MASS : 528 (M+1)

Example 50-38)

[0225]

IR (Neat) : 3250, 1670, 1625, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 1.04-1.25 (3H, m); 2.16-4.90 (10H, m); 3.61 (3H, s); 6.60-8.27 (8H, m); 10.84 (1H, s); 11.09 (1H, s)
MASS : 557 (M+1)

Example 50-39)

[0226]

$[\alpha]_D^{19}$: -8.8° (C=1.0, MeOH)
IR (Neat) : 3300, 1680, 1630, 1280 cm^{-1}
NMR (DMSO-d_6, δ) : 1.0-1.2 (3H, m); 2.10-4.93 (10H, m); 6.6-8.24 (8H, m); 10.83 (1H, s)
MASS : 527 (M+1)

Example 50-40)

[0227]

$[\alpha]_D^{19}$: -16.5° (C=1.0, MeOH)
IR (Neat) : 3300, 1630, 1460, 1370, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 0.94-1.15 (3H, m); 2.15-5.0 (18H, m); 6.6-8.2 (8H, m); 10.88 (1H, s); 11.30 (1H, br s)
MASS : 610 (M+1) **(free)**

Example 50-42)

[0228]

mp : 194-198°C (dec.)
$[\alpha]_D^{29}$: -11.2° (C=0.5, DMF)
IR (Nujol) : 3700-3150, 3000-2100, 1726, 1637, 1274, 1131; 896 cm^{-1}
NMR (DMSO-d_6, δ) : 1.80-4.40 (24H, m); 6.50-8.20 (8H, - m); 10.85 (1H, s)
MASS : 610 (M+1) (free)

Example 50-48)

[0229]

$[\alpha]_D^{20}$: -11.0° (C=1.0, MeOH)
IR (Nujol) : 3350, 3150, 2650, 2450, 2300, 1635, 1270 cm^{-1}
NMR (DMSO-d_6, δ) : 1.60-4.93 (26H, m); 6.60-8.66 (8H, m); 9.18 (1H, s); 10.87 (1H, s)
MASS : 639 (M+1)

Example 50-49)

[0230]

IR (Nujol) : 3200, 1626 cm^{-1}
NMR(DMSO-d_6, δ) : 1.86-2.12 (7H, m); 2.34-2.59 (4H, m); 2.82-5.20 (15H, m); 6.60-8.28 (13H, m); 10.96 (1H, s); 10.87-11.35 (1H, m)
MASS : 699 (M+1) (free)

Example 50-50)

[0231]

IR (Nujol) : 3350-3210, 2550-2500, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 1.76-2.20 (2H, m); 2.37-2.66 (2H, m); 2.80-5.20 (19H, m); 6.59-8.30 (13H, m); 10.97 (1H, s); 10.87-11.55 (2H, m)
MASS : 686 (M+1) (free)

Example 50-51)

[0232]

IR (Nujol) : 3350-3250, 2580, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 0.95-2.20 (12H, m); 2.76-5.20 (22H, m); 6.54-8.30 (8H, m); 10.96 (1H, s); 10.79-11.17 (1H, m); 11.42 (1H, br s)
MASS : 692 (M+1) (free)

Example 50-52)

[0233]

IR (Neat) : 3330, 2680, 1630, 1540 cm^{-1}
NMR (DMSO-d_6, δ) : 1.75-2.37 (4H, m); 2.76, 2.78 (6H, 2 s); 2.92-5.20 (15H, m); 6.55-8.47 (9H, m); 10.37 (1H, br s); 10.97 (1H, s); 11.15-11.57 (1H, br s)
MASS : 612 (M+1) (free)

Example 50-53)

[0234]

IR (Nujol) : 3200, 1626 cm^{-1}
NMR (DMSO-d_6, δ) : 1.20-1.67 (6H, m); 1.72-2.12 (2H, m); 2.23-2.52 (2H, m); 2.75-5.18 (15H, m); 6.57-8.27 (8H, m); 10.95 (1H, s); 10.80-11.36 (1H, m)
MASS : 609 (M+1) (free)

Example 50-54)

[0235]

IR (Nujol) : 3350-3230, 1640 cm^{-1}
NMR (DMSO-d_6, δ) : 1.92-2.14 (2H, m); 2.44-2.66 (2H, m); 2.96-5.20(19H, m); 6.57-8.26 (12H, m); 10.97 (1H, s); 10.88-11.04 (2H, m); 11.36-11.65 (1H, m)
MASS : 687 (M+1) (free)

Example 50-55)

[0236]

IR (Nujol) : 3400-3220, 2550, 1625 cm^{-1}
NMR (DMSO-d_6, δ) : 1.29-2.26 (6H, m); 2.38-5.22 (18H, m); 6.58-8.30 (13H, m); 10.96 (1H, s); 10.79-11.30 (1H, m)
MASS : 685 (M+1) (free)

Example 50-56)

[0237]

IR (Neat) : 3260, 2990, 2810, 1625 cm^{-1}
NMR (DMSO-d_6, δ) : 1.47-2.22 (9H, m); 2.58-4.96 (14H, m); 6.56-8.26 (23H, m); 10.85 (1H, s)
MASS : 852 (M+1)

Example 50-57)

[0238]

IR (Nujol) : 3330, 2700, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.80-2.23 (2H, m); 2.33-2.66 (2H, m); 2.90-5.20 (19H, m); 6.55-8.28 (8H, m); 9.20-9.80 (2H, m); 10.97 (1H, s); 10.86-11.63 (1H, m)
MASS : 610 (M+1) (free)

Example 50-58)

[0239]

mp : 180-185°C
$[\alpha]_D^{30}$: -21.3° (C=1.0, MeOH)

Example 52

[0240] The following piperazine derivatives (Table 3) were prepared by the similar manner to that of the each Example No. defined in the "Process" column. The physical properties of the object compounds are shown after the table.

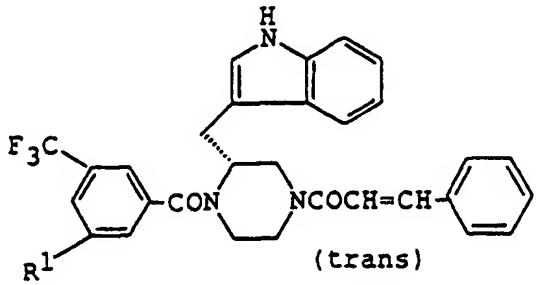


Table 3

Example No.	Object Compounds		Starting Compound	Process
	R^1	Salt		
52-1)	$-NO_2$	-	Pr. 17	Ex. 1
52-2)	-NHCHO	-	Pr. 17	Ex. 1

Table 3 (continued)

Example No.	Object Compounds		Starting Compound	Process
	R^1	Salt		
52-4)	$-N(CH_3)_2$	-	Pr. 17	Ex. 1
52-5)	$-NHSO_2CH_3$	-	Ex.52-6)	Prep. Ex. 40
52-6)	$-NHCOCH_3$	-	Ex. 64	Prep. Ex. 40
52-7)	$-NHCH_3$	-	Ex.52-3)	Ex. 64

[0241] Physical properties of the compounds of the Example 52 :

Example 52-1)

[0242]

$[\alpha]_D^{18}$: +8.7° (C=1.0, MeOH)
IR (Neat) : 3260, 1635, 1540, 1420, 1310 cm^{-1}
NMR (DMSO-d_6, δ) : 2.74-5.07 (11H, m); 6.57-8.59 (13H, m); 10.91 (1H, s)
MASS : 563 (M+1)

Example 52-2)

[0243]

$[\alpha]_D^{19}$: -25.1° (C=1.0, MeOH)
IR (Neat) : 3250, 1690, 1640, 1600, 1430, 1340-1270 cm^{-1}
NMR D(DMSO-d_6, δ) : 2.85-5.13 (11H, m); 6.57-8.44 (9H, m); 10.33-10.96 (2H, in)
MASS : 561 (M+1)

Example 52-4)

[0244]

$[\alpha]_D^{18}$: +10.1° (C=1.0, MeOH)
IR (Neat) : 3250, 1640, 1600, 1490, 1425 cm^{-1}
NMR (DMSO-d_6, δ) : 2.83-5.14 (11H, m); 2.94 (6H, s); 6.52-7.84 (13H, m); 10.85 (1H, s)

Example 52-5)

[0245]

$[\alpha]_D^{18}$: -43.7° (C=1.0, MeOH)
IR (Neat) : 3400, 3250, 1640, 1600, 1430, 1330 cm^{-1}
NMR (DMSO-d_6, δ) : 2.86-5.10 (11H, m); 3.0 (3H, s); 6.64-7.88 (12H, m); 10.2-10.4 (1H, m); 10.85 (1H, s)
MASS : 611 (M+1)

Example 52-6)

[0246]

$[\alpha]_D^{18}$: -27.2° (C=1.0, MeOH)
IR (Neat) : 3275, 1680, 1640, 1600, 1560, 1425 cm^{-1}
NMR (DMSO-d_6, δ) : 2.08 (3H, s); 2.8-5.09 (11H, m); 6.6-8.11 (14H, m); 10.83 (1H, s)
MASS : 575 (M+1)

Example 52-7)

[0247]

IR (Neat) : 3300, 1640, 1600, 1460, 1420 cm^{-1}
NMR (DMSO-d_6, δ) : 2.64-5.1 (14H, m); 6.55-7.83 (14H, m); 10.85 (1H, s)
MASS : 547 (M+1)

Example 54

[0248] The following piperazine derivatives (Table 5) were prepared by the similar manner to that of the each Example No. defined in the "Process" column. The physical properties of the object compounds are shown after the table.

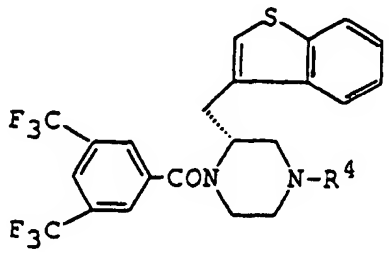


Table 5

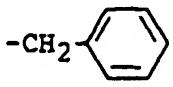
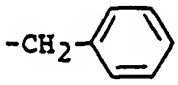
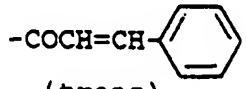
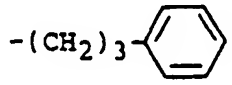
Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
54-1)		-	Pr.8-5)	Ex. 1
54-2)		HCl	Ex.54-1)	Ex. 23
54-3)	-H	-	Ex.54-1)	Ex. 6

Table 5 (continued)

Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
54-4)	 (trans)	-	Ex. 69	Prep. Ex. 16
54-5)		HCl	Ex.54-3)	Ex. 11

[0249] Physical properties of the compounds of the Example 54 :

Example 54-1)

[0250]

IR (Neat) : 3100-2700, 1635, 1490, 1430, 1380, 1350 cm^{-1}
NMR ($CDCl_3$, δ) : 2.0-2.4 (2H, m); 2.8-3.8 (8H, m); 4.0-5.2 (1H, m); 6.8-8.2 (13H, m)
MASS : 563 (M+1)

Example 54-2)

[0251]

mp : 150-165°C
IR (Nujol) : 3400, 2200-2700, 1635, 1440, 1360 cm^{-1}
NMR (DMSO-d_6, δ) : 3.0-4.3 (9H, m); 4.5-5.2 (2H, m); 6.9-7.3 (2H, m); 7.4-8.3 (10H, m)
MASS : 563 (M+1) (free)

Example 54-3)

[0252]

IR (Neat) : 3300, 2700-3100, 1630, 1430, 1370, 1350 cm^{-1}
MASS : 473 (M+1)

Example 54-4)

[0253]

mp : 60-63°C
$[\alpha]_D^{23}$: -25.2° (C=1.0, MeOH)
IR (Nujol) : 1635, 1605, 1450, 1350, 1315 cm^{-1}
NMR ($CDCl_3$, δ) : 2.8-5.4 (9H, m); 6.8-8.3 (15H, m)
MASS : 603 (M+1), 575, 473

Example 54-5)

[0254]

mp : 124-130°C (dec.)
$[\alpha]_D^{20}$: +4.0° (C=0.05, MeOH)
IR (Nujol) : 3300, 2300-2600, 1635, 1430, 1360 cm^{-1}
NMR (DMSO-d_6, δ) : 2.0-2.3 (2H, m); 2.6-2.8 (2H, m); 3.0-4.0 (11H, m); 4.2-5.3 (1H, m); 7.0-7.6 (9H, m); 7.8-8.4 (4H, m); 11.0-11.6 (1H, m)
MASS : 591 (M+1), 563

Example 55

[0255] The following piperazine derivatives (Table 6) were prepared by the similar manner to that of the each Example No. defined in the "Process" column. The physical properties of the object compounds are shown after the table.

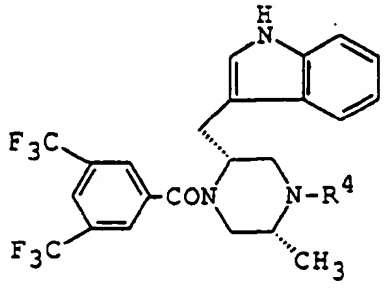
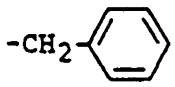
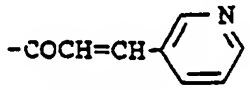
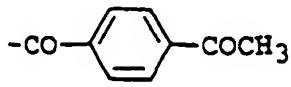


Table 6

Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
55-1)		-	Pr.8-8)	Ex. 1
55-2)	-H	-	Ex.55-1)	Ex. 6
55-3)	 (trans)	-	Ex.55-2)	Prep. Ex. 16
55-5)		-	Ex.55-2)	Ex. 16

[0256] Physical properties of the compounds of the Example 55 :

Example 55-1)

[0257]

$[\alpha]_D^{19}$: -43.2° (C=1.0, MeOH)
IR (Neat) : 3400, 3300, 1630, 1440, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 1.09-1.32 (3H, m); 2.35-4.8 (10H, m); 6.53-8.45 (10H, m); 10.69 (1H, s)
MASS : 560 (M+1)

Example 55-2)

[0258]

mp : 157-159°C
IR (Nujol) : 3260, 1625, 1600, 1460, 1280 cm^{-1}
NMR (DMSO-d_6, δ) : 9.3-1.18 (3H, m); 2.6-4.85 (8H, m); 6.65-8.4 (9H, m); 10.86 (1H, s)
MASS : 470 (M+1)

Example 55-3)

[0259]

$[\alpha]_D^{19}$: -107.3° (C=1.0, MeOH)
IR (Neat) : 3250, 1630, 1610, 1430, 1340, 1280 cm^{-1}
NMR (DMSO-d_6, δ) : 0.86-1.4 (3H, m); 2.88-5.16 (10H, m); 6.6-8.86 (12H, m); 10.92 (1H, d, J=14Hz)
MASS : 601 (M+1)

Example 55-5)

[0260]

$[\alpha]_D^{20}$: -107.5° (C=1.0, MeOH)
IR (Neat) : 3260, 1680, 1625, 1425, 1350, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 0.9-1.2 (3H, m); 2.56 (3H, s); 2.7-4.9 (8H, m); 6.86-8.2 (12H, m); 10.8 (1H, s)
MASS : 616 (M+1)

Example 56

[0261] The following piperazine derivatives (Table 7) were prepared by the similar manner to that of the each Example No. defined in the "Process" column. The physical properties of the object compounds are shown after the table.

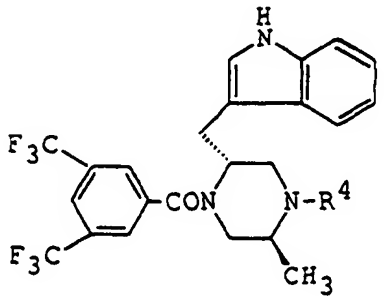
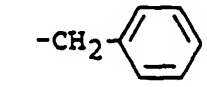
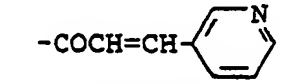


Table 7

Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
56-1)		-	Pr.8-9)	Ex. 1
56-2)	-H	-	Ex.56-1)	Ex. 6
56-3)	 (trans)	-	Ex.56-2)	Prep. Ex. 16
56-4)	$-CH_2COOCH_3$	-	Ex.56-2)	Ex. 11
56-5)	$-CH_2CONH_2$	-	Ex.56-4)	Prep. Ex. 9

[0262] Physical properties of the compounds of the Example 56 :

Example 56-1)

[0263]

$[\alpha]_D^{19}$: -9.6° (C=1.0, MeOH)
IR (Neat) : 3250, 1655, 1625, 1430, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 1.12 (3H, d, J=7Hz); 2.35-4.82 (10H, m); 6.57-8.40 (10H, m); 10.74 (1H, s)
MASS : 560 (M+1)

Example 56-2)

[0264]

IR (Neat) : 3250. 1620, 1430, 1350, 1275 cm^{-1}

NMR (DMSO-d_6, δ) : 1.13 (3H, s); 1.68-3.55 (8H, m); 4.46 (1H. br s); 6.72-8.48 (8H, m); 10.86 (1H, s)
MASS : 470 (M+1)

Example 56-3):

[0265]

$[\alpha]_D^{19}$: +27.0° (C=1.0, MeOH)
IR (Neat) : 3250, 1640, 1430, 1280 cm^{-1}
NMR (DMSO-d_6, δ) : 1.1-1.4 (3H, m); 2.8-5.1 (10H, m); 6.6-8.94 (12H, m); 10.90 (1H, d, J=14Hz)
MASS : 601 (M+1)

Example 56-4)

[0266]

IR (Neat) : 3300, 1740, 1670, 1625, 1435, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 0.8-1.1 (3H, m); 2.6-4.8 (8H, m); 2.89 (3H, s); 3.70 (2H, s); 6.44-8.56 (8H, m); 10.84 (1H, s)
MASS : 542 (M+1)

Example 56-5)

[0267]

mp : 245-247°C
$[\alpha]_D^{18}$: +3.1° (C=1.0, MeOH)
IR (Nujol) : 3425, 3300, 3150, 1675, 1625, 1460, 1270 cm^{-1}
NMR (DMSO-d_6, δ) : 0.8-1.1 (3H, m); 2.41-4.86 (10H, m); 6.57-8.22 (8H, m); 10.84 (1H, s)
MASS : 527 (M+1)

Example 58

[0268] The following piperazine derivatives (Table 9) were prepared by the similar manner to that of the each Example No. defined in the "Process" column. The physical properties of the object compounds are shown after the table.

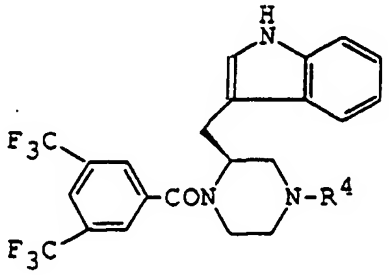
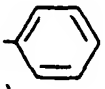


Table 9

Example No.	Object Compounds		Starting Compound	Process
	R^4	Salt		
58-1)	-COCH=CH-  (trans)	-	Ex. 7-8)	Ex. 20
58-2)	$-CH_2CONH_2$	-	Ex.58-3)	Prep. Ex. 9
58-3)	$-CH_2COOCH_3$	-	Ex. 7-8)	Ex. 11

[0269] Physical properties of the compounds of the Example 58 :

Example 58-1)

[0270]

$[\alpha]_D^{26}$: +32.1° (C=1.0, MeOH)
IR (Film) : 3275, 1635, 1430 cm^{-1}
NMR (DMSO-d_6, δ) : 2.8-5.1 (9H, m); 6.6-8.2 (15H, m); 10.9 (1H, s)
MASS : 586 (M+1)

Example 58-2)

[0271]

mp : >240°C
$[\alpha]_D^{18}$: +5.8° (C=1.0, MeOH)
IR (Nujol) : 3440, 3300, 3150, 1675, 1625, 1460, 1270 cm^{-1}
NMR (DMSO-d_6, δ) : 2.09-4.93 (11H, m); 6.67-8.24 (8H, m); 10.83 (1H, s)
MASS : 513 (M+1)

Example 58-3)

[0272]

IR (Neat) : 3300. 1740, 1625, 1435, 1275 cm^{-1}
NMR (DMSO-d_6, δ) : 2.28-4.91 (9H, m); 2.51 (3H, s); 3.64 (2H, s); 6.6-8.2 (8H, m); 10.85 (1H, s)
MASS : 528(M+1)

Example 60

[0273] The following piperazine derivatives (Table 11) were prepared by the similar manner to that of the each Example No. defined in the "Process" column. The physical properties of the object compounds are shown after the table.

Table 11

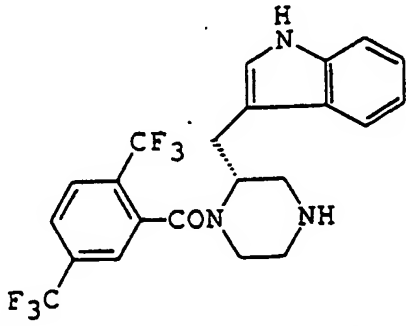
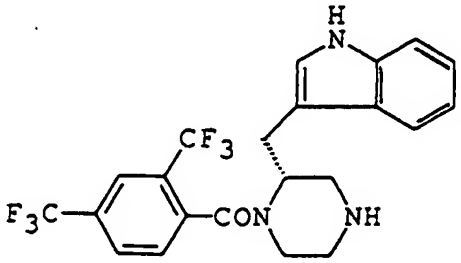
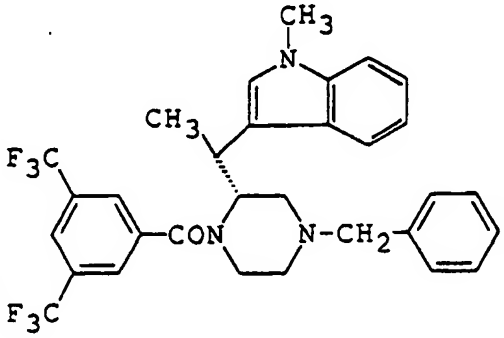
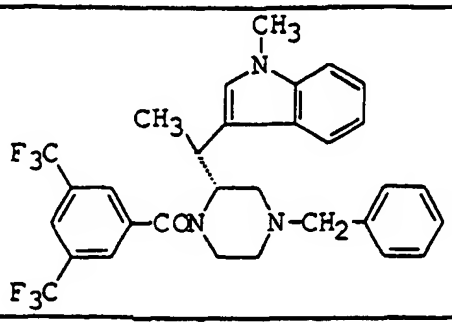
Example No.	Object Cmpounds	Salt	Starting Compound	Process
60-1)		-	Ex. 4-5)	Ex. 6
60-2)		-	Ex. 4-6)	Ex. 6
60-3)		-	Pr.8-7)	Ex.1

Table 11 (continued)

Example No.	Object Compounds	Salt	Starting Compound	Process
60-4)		HCl	Ex.60-3)	Ex.23

[0274] Physical properties of the compounds of the Example 60 :

Example 60-1)

[0275]

IR (Nujol) : 3200, 1620, 1610, 1320 cm^{-1}
NMR (DMSO-d_6, δ) : 2.4-4.9 (9H, m); 6.7-8.1 (8H, m); 10.8 (1H, s); 10.87 (1H, s)
MASS : 456 (M+1)

Example 60-2)

[0276]

$[\alpha]_D^{25}$: +54.1° (C=1.0, MeOH)
IR (Film): 3250, 1620, 1430, 1340 cm^{-1}
NMR (DMSO-d_6, δ) : 2.1-4.8 (9H, m); 6.3-8.3 (8H, m); 10.88 (1H, s); 10.93 (1H, s)
MASS : 456 (M+1)

Example 60-3)

[0277]

IR (Neat) : 3100-2700 (m), 1640, 1440, 1380, 1350 cm^{-1}
NMR ($CDCl_3$, δ) : 1.1-1.4 (3H, m); 1.6-1.8 (1H, m); 1.8-2.0 (1H, m); 2.2-2.4 (1H, m); 2.7-3.0 (1H, m); 3.1-5.0 (6H, m); 3.61 (3H, s); 6.8-8.5 (13H, m)
MASS : 574 (M+1)

Example 60-4)

[0278]

mp : 130-131°C (dec.)
$[\alpha]_D^{23}$: -0.4° (C=0.5, MeOH)

IR (Nujol) : 3350, 2700-2400, 1640, 1450, 1350 cm^{-1}
NMR (DMSO-d_6, δ) : 1.0-1.4 (3H, m); 3.0-5.1 (10H, m); 3.65 (3H, s); 6.6-8.5 (13H, m); 11.2-11.6 (1H, m)

Example 61

[0279] To a stirred mixture of 4-(dimethylamino)butyric acid hydrochloride (70 mg) and 1-hydroxybenzotriazole hydrate (160 mg) in dichloromethane (10 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (80 mg) under ice cooling. After stirring for 30 minutes, a solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (200 mg) in dichloromethane (5 ml) was added at the same temperature. The resulting mixture was stirred for 2.5 hours at room temperature. Dichloromethane and aqueous sodium bicarbonate solution were added to the reaction mixture and then the organic layer was separated and dried over magnesium sulfate. Evaporation of the solvent in vacuo gave (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[4-(dimethylamino)butyryl]-2-(1H-indol-3-yl-methyl)piperazine (0.25 g).

IR (Neat) : 3270, 2920, 2860, 2820, 2770, 1630 cm^{-1}
NMR (DMSO-d_6, δ) : 1.52-1.83 (2H, m); 2.09, 2.10, 2.13 (6H, 3 s); 2.00-5.10 (13H, m); 6.53-8.25 (8H, m); 10.89 (1H, s)
MASS : 569 (M+1)

Example 62

[0280] Cyclohexyl isocyanate (0.06 ml) was added to a stirred solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.2 g) in dichloromethane (10 ml) at room temperature. After stirring for 4 hours, dichloromethane (10 ml) and water (5 ml) were added. The organic layer was separated, washed with brine and dried over magnesium sulfate. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol (98:2) to give (2R)-1-[3,5-bis(trifluoromethyl) benzoyl]-4-cyclohexylcarbamoyl-2-(1H-indol-3-yl-methyl)piperazine (0.18 g).

IR (Neat) : 3280, 2920, 2840, 1622, 1525 cm^{-1}
NMR (DMSO-d_6, δ) : 1.00-1.90 (10H, m); 2.76-4.90 (10H, m); 6.13-8.23 (9H, m); 10.87 (1H, s)
MASS : 581 (M+1)

Example 63

[0281] To a stirred solution of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (400 mg) in dichloromethane (5 ml) was added 1,1'-carbonyldiimidazole (140 mg) at room temperature. The resulting mixture was stirred overnight. Additional 1,1'-carbonyldiimidazole (70 mg) was added to the mixture and then stirred for 1 hour. After the dichloromethane was removed under reduced pressure, N-methylpropylamine (1 g) was added. The mixture was stirred at room temperature for 2 hours and then at reflux temperature for 12 hours. After cooling, dichloromethane and water were added to the reaction mixture. The organic layer was separated, washed with aqueous 0.5N hydrochloric acid and brine. After evaporation of the solvent, the residue was purified by column chromatography on silica gel, eluting with a mixture of dichloromethane and methanol (99:1) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(N-methyl-N-propylcarbamoyl)piperazine (0.18 g).

IR (Neat) : 3260, 2950, 2910, 2850, 1628 cm^{-1}
NMR (DMSO-d_6, δ) : 0.83 (3H, t, J=7.2Hz); 1.38-1.67 (2H, m); 2.85 (3H, s); 2.69-5.04 (11H, m); 6.58-8.29 (8H, m); 10.86 (1H, s)
MASS : 555 (M+1)

Example 64

[0282] A mixture of (2R)-4-(trans-cinnamoyl)-1-[3-formylamino-5-(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl) piperazine (280 mg) and aqueous 10% hydrochloric acid (1 ml) in methanol (10 ml) was stirred at room temperature for 6 hours. The mixture was evaporated under reduced pressure. The resulting powder was collected by filtration and dried to give (2R)-1-[3-amino-5-(trifluoromethyl)benzoyl]-4-(trans-cinnamoyl)-2-(1H-indol-3-yl-methyl)piperazine hydrochloride (280 mg).

$[\alpha]_D^{18}$: -22.8° (C=1.0, MeOH)

IR (Neat) : 3250, 2850, 2050, 1635, 1600, 1430, 1335 cm^{-1}
NMR (DMSO-d_6, δ) : 2.78-5.54 (14H, m); 6.67-7.85 (13H, m); 10.89 (1H, s)
MASS : 533 (M+1) (free)

Example 65

[0283] Hydrochloric acid (0.22 ml) was added to a stirred mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[N-(2-hydroxybenzylidene)-2-aminoethyl]-2-(1H-indol-3-yl-methyl)piperazine (0.80 g), ethyl acetate (12 ml) and methanol (6 ml) at room temperature. The mixture was stirred at 50°C for 4.5 hours and then concentrated in vacuo to give an oil. The oil was treated with 4N hydrogen chloride in dioxane solution (0.33 ml) to afford (2R)-4-(2-aminoethyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine dihydrochloride (0.57 g).

IR (Neat) : 3340, 2930, 1625 cm^{-1}
NMR (DMSO-d_6, δ) : 2.92-5.20 (13H, m); 6.48-8.85 (11H, m); 10.98 (1H, s); 11.52-11.90 (1H, m)
MASS : 499 (M+1) (free)

Example 66

[0284] Sodium azide (0.21 g) was added to a stirred mixture of (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-(cyanomethyl)-2-(1H-indol-3-yl-methyl)piperazine (0.32 g) and ammonium chloride (0.17 g) in dimethylformamide (5 ml). The mixture was stirred at 115°C for 16 hours. Additional sodium azide and ammonium chloride were added to the reaction mixture until the starting material was consumed. After cooling, the mixture was poured into ice-cold water. The resulting precipitate was collected by filtration, washed with water and dried. The precipitate was treated with 4N hydrogen chloride in dioxane solution to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(1H-tetrazol-5-yl-methyl)piperazine hydrochloride (0.19 g).

IR (Nujol) : 3280, 2700-2300, 1635 cm^{-1}
NMR (DMSO-d_6, δ) : 2.75-5.12 (11H, m); 6.54-8.30 (8H, m); 10.94 (1H, s)
MASS.: 538 (M+1) (free)

Example 67

[0285] To a stirred mixture of (2R)-4-(3-aminopropyl)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)piperazine (0.20 g) and triethylamine (0.06 ml) in tetrahydrofuran (10 ml) was added 4-nitrophenyl chloroformate (0.08 g) under ice-cooling. After 35 minutes, the resulting precipitate was filtered off. To the filtrate were added triethylamine (0.06 ml) and 30% methylamine in ethanol (0.05 ml) at room temperature. After stirring for 1 hour and 40 minutes, additional 30% methylamine in ethanol (0.05 ml) was added to the reaction mixture and then stirred for 45 minutes. The reaction mixture was concentrated in vacuo and the residue was partitioned between dichloromethane and water. The organic layer was separated, washed with aqueous saturated sodium chloride solution and dried over magnesium sulfate. After evaporation of the solvent in vacuo, the residue was purified by column chromatography on silica gel eluting with a mixed solvent of dichloromethane and methanol (100:3). The eluate was treated with 4N hydrogen chloride in dioxane solution to afford (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[3-(3-methylureido)propyl]-piperazine hydrochloride (0.08 g).

IR (Nujol) : 3240, 2580, 1633 cm^{-1}
NMR (DMSO-d_6, δ) : 1.72-2.03 (2H, m); 2.55, 2.56 (3H, 2 s); 2.92-5.21 (15H, m); 6.60-8.29 (8H, m); 10.97 (1H, s); 11.12-11.45 (1H, m)
MASS : 570 (M+1) (free)

Example 69

[0286] To a stirred solution of (2R)-2-(benzo[b]thiophen-3-yl-methyl)-4-benzyl-1-[3,5-bis(trifluoromethyl)benzoyl]piperazine (0.75 g) in dichloromethane (8 ml) was added dropwise 1-chloroethyl chloroformate (0.19 ml) at ice-bath temperature. The resulting mixture was stirred at room temperature for 1 hour and then at reflux temperature for 5 hours. The reaction mixture was evaporated under reduced pressure. Methanol (5 ml) was added to the residue and the whole mixture was heated under refluxing for 1 hour. The mixture was concentrated in vacuo and the residue was partitioned between aqueous sodium bicarbonate solution (10 ml) and ethyl acetate (20 ml). The organic layer was separated, washed with brine and dried over magnesium sulfate. After evaporation of the solvent in vacuo, the residue was treated

with 4N hydrogen chloride in ethyl acetate solution to afford (2R)-2-(benzo[b]thiophen-3-yl-methyl)-1-[3,5-bis(trifluoromethyl)benzoyl]piperazine hydrochloride (0.69 g).

mp : 145-155°C
$[\alpha]_D^{24}$: +5.38° (C=0.13, MeOH)
IR (Nujol) : 3300, 2900-2400, 1625, 1430, 1350 cm^{-1}
NMR (DMSO-d_6, δ) : 3.0-4.0 (9H, m); 4.2-4.3 (1H, m); 7.0-8.4 (8H, m); 9.5-10.2 (1H, m)
MASS : 473 (M+1) (free)

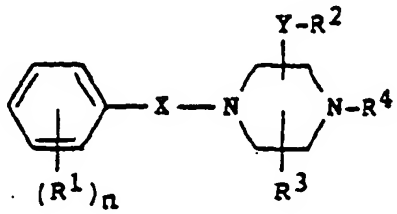
Example 72

[0287] To a mixture of (2R)-1-[3,5-his(trifluoromethyl)benzoyl]-4-(3-carboxypropyl)-2-(1H-indol-3-yl-methyl)piperazine (180 mg), 4-piperidinopiperidine (56 mg) and 1-hydroxybenzotriazole hydrate (45 mg) in dichloromethane (4 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (64 mg) at ice-bath temperature. After stirring for 30 minutes, the reaction mixture was allowed to warm to room temperature and was stirred for 2 hours and 40 minutes. The reaction mixture was concentrated under reduced pressure and the resulting residue was partitioned between ethyl acetate and water. The organic layer was washed successively with aqueous saturated sodium bicarbonate and brine, and dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by column chromatography on silica gel eluting with a mixture of dichloromethane and methanol (10:1) to give (2R)-1-[3,5-bis(trifluoromethyl)benzoyl]-4-[3-(4,1'-bipiperidin-1-yl-carbonyl)propyl]-2-(1H-indol-3-yl-methyl)piperazine, which was converted to the corresponding dihydrochloride salt (0.18 g) by treatment with 4N hydrogen chloride in dioxane solution.

IR (Nujol) : 3350, 2630, 1626 cm^{-1}
NMR (DMSO-d_6, δ) : 1.17-2.24 (12H, m); 2.34-5.22 (22H, m); 6.57-8.29 (8H, m); 10.22-10.60 (1H, m); 10.97 (1H, s); 10.83-11.57 (1H, m)
MASS : 692 (M+1) (free)

Claims

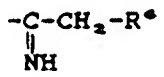
1. A compound of the following general formula :



wherein

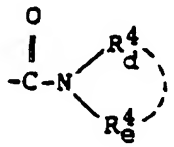
X is carbonyl;
Y is bond or (C_1-C_6)alkylene;
R^1 is halogen, (C_1-C_6)alkyl, halo (C_1-C_6)alkyl, C_6-C_{10} aryloxy, nitro, amino, (C_1-C_6)alkylamino, di(C_1-C_6) alkylamino, (C_1-C_6)alkanoylamino or (C_1-C_6)alkanesulfonylamino;
R^2 is aromatic hetero (mono- or bi)cyclic group containing one nitrogen or sulfur atom which may be substituted by a substituent selected from a group consisting of (C_1-C_6)alkyl and di (C_1-C_6)alkylamino (C_1-C_6)alkyl;
R^3 is hydrogen or (C_1-C_6)alkyl;
R^4 is

(i) a group of the formula $-SO_2-R^5$ in which R^5 is (C_1-C_6) alkyl
(ii) a group of the formula



in which R^6 is $(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, or
(iii) a group of the formula -A-Z in which A is bond, $(C_1\text{-}C_6)$alkylene or $(C_2\text{-}C_6)$alkenylene,

Z is hydrogen;
nitrile;
amino;
cyclo $(C_3\text{-}C_6)$ alkyl;
$(C_1\text{-}C_6)$aryl;
$C_6\text{-}C_{10}$ aryloxy;
carboxy;
$(C_1\text{-}C_6)$alkoxycarbonyl which may be substituted by $C_6\text{-}C_{10}$ aryl;
$(C_1\text{-}C_6)$alkanoyl which may be substituted by a substituent selected from a group consisting of $C_6\text{-}C_{10}$ aryl, halo$(C_6\text{-}C_{10})$aryl, $C_6\text{-}C_{10}$ aryloxy,
$(C_1\text{-}C_6)$alkoxy, halogen, amino, di $(C_1\text{-}C_6)$alkylamino,
$(C_1\text{-}C_6)$aroylamino,
cyclo $(C_3\text{-}C_6)$alkyl, and aromatic hetero(mono- or bi-)cyclic group containing one nitrogen atom;
halo $(C_1\text{-}C_6)$alkylcarbonyl;
cyclo $(C_3\text{-}C_6)$alkylcarbonyl;
$(C_2\text{-}C_6)$alkenoyl which may be substituted by a substituent selected from a group consisting of $C_6\text{-}C_{10}$ aryl, dihalo $(C_6\text{-}C_{10})$aryl, $C_6\text{-}C_{10}$ aroyl,
cyclo $(C_3\text{-}C_6)$alkyl and aromatic hetero(mono- or bi-)cyclic group containing one nitrogen atom;
$C_6\text{-}C_{10}$ ar$(C_2\text{-}C_6)$alkynoyl;
carbamoyl derivative illustrated by the formula



(wherein R^4_d and R^4_e are independently hydrogen; $(C_1\text{-}C_6)$alkyl which may be substituted by a substituent selected from a group consisting of $C_6\text{-}C_{10}$ aryl, halo$(C_6\text{-}C_{10})$aryl, $(C_1\text{-}C_6)$alkoxy, hydroxy, carbamoyl, $C_6\text{-}C_{10}$ ar$(C_1\text{-}C_6)$alkoxycarbonyl, di$(C_1\text{-}C_6)$alkylamino, saturated heterocyclic group containing one nitrogen atom, carboxy, cyclo $(C_3\text{-}C_6)$alkyl and aromatic hetero(mono)cyclic group containing one nitrogen atom; or saturated heterocyclic group containing two nitrogen atoms substituted by $(C_1\text{-}C_6)$ alkyl, or R^4_d and R^4_e together with the nitrogen atom form a saturated heterocyclic group containing one or two nitrogen atom(s) which may be substituted by 1 or 2 and same or different substituent(s) selected from a group consisting of $C_6\text{-}C_{10}$ aryl, $(C_1\text{-}C_6)$alkyl, hydroxy$(C_1\text{-}C_6)$alkyl, $(C_6\text{-}C_{10})$ar$(C_1\text{-}C_6)$alkyl, carbamoyl, cyclo$(C_3\text{-}C_6)$alkyl, carboxy$(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoylamino, oxo, $(C_1\text{-}C_6)$alkoxycarbonyl, saturated heterocyclic group containing one nitrogen atom and aromatic hetero(mono)cyclic group containing one nitrogen atom;
$C_6\text{-}C_{10}$ aroyl which may be substituted by 1 or 2 and same or different substituent(s) selected from a group consisting of carboxy, cyano, halogen, hydroxy, $(C_1\text{-}C_6)$alkanoyl, $(C_1\text{-}C_6)$alkanoyloxy, amino, di$(C_1\text{-}C_6)$ alkylamino, $(C_1\text{-}C_6)$alkanoylamino, $(C_1\text{-}C_6)$alkanesulfonylamino, nitro and $(C_1\text{-}C_6)$alkoxycarbonyl;
aromatic hetero(mono)cyclic carbonyl group containing one or two nitrogen atom(s);
aromatic hetero(bi)cyclic carbonyl group containing one nitrogen or oxygen atom; or saturated heterocyclic carbonyl group containing one nitrogen atom which is substituted by 1 or 2 and same or different substituent (s) selected from a group consisting of hydroxy and $(C_1\text{-}C_6)$alkoxycarbonyl;
$(C_1\text{-}C_6)$alkanoylamino;
$(C_1\text{-}C_6)$alkoxycarbonylamino;
$(C_1\text{-}C_6)$alkanesulfonylamino;
$C_6\text{-}C_{10}$ arylsulfonylamino;
hetero(mono- or bi-)cyclic group containing one nitrogen atom;

and

n is 0, 1 or 2;
provided that when n is 2, these R^1 may be the same or different group respectively;
or its pharmaceutically acceptable salt.

2. The compound of claim 1, in which

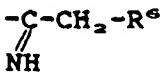
R^1 is halogen, $(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, phenyloxy, nitro, amino, $(C_1$-$C_6)$alkanoylamino, di$(C_1$-$C_6)$alkylamino, $(C_1$-$C_6)$alkanoylamino or $(C_1$-$C_6)$alkanesulfonylamino;

R^2 is benzothienyl or indolyl which may be substituted by a substituent selected from a group consisting of $(C_1$-$C_6)$alkyl and
di$(C_1$-$C_6)$alkylamino$(C_1$-$C_6)$alkyl;

R^4 is

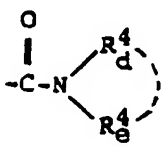
(i) a group of the formula $-SO_2-R^5$ in which R^5 is $(C_1$-$C_6)$alkyl,

(ii) a group of the formula



in which R^6 is $(C_1$-$C_6)$alkoxyphenyl, or

(iii) a group of the formula - A - Z in which A is bond, $(C_1$-$C_6)$alkylene or $(C_2$-$C_6)$alkenylene;
Z is hydrogen;
nitrile;
amino;
cyclo$(C_3$-$C_6)$alkyl;
phenyl;
phenyloxy;
carboxy;
$(C_1$-$C_6)$alkoxycarbonyl which may be substituted by phenyl;
$(C_1$-$C_6)$ alkanoyl which may be substituted by a substituent selected from a group consisting of phenyl, halophenyl, phenyloxy, $(C_1$-$C_6)$alkoxy, halogen, amino, di$(C_1$-$C_6)$alkylamino and benzoylamino,
cyclo$(C_3$-$C_6)$alkyl;
halo$(C_1$-$C_6)$alkylcarbonyl;
cyclo$(C_3$-$C_6)$alkylcarbonyl;
$(C_2$-$C_6)$alkenoyl which may be substituted by a substituent selected from a group consisting of phenyl, dihalophenyl, benzoyl and cyclo$(C_3$-$C_6)$alkyl;
phenyl$(C_2$-$C_6)$alkynoyl;
carbamoyl derivative illustrated by the formula:



(wherein $R^4{}_d$ and $R^4{}_e$ are independently hydrogen; $(C_1$-$C_6)$alkyl which may be substituted by a substituent selected from a group consisting of phenyl, halophenyl, $(C_1$-$C_6)$alkoxy, hydroxy, carbamoyl, phenyl$(C_1$-$C_6)$alkoxycarbonyl, di$(C_1$-$C_6)$alkylamino,

carboxy and cyclo(C_3-C_6)alkyl; or
(C_1-C_6)alkylpiperazinyl, or $R^4{}_d$ and $R^4{}_e$ together with the nitrogen atom form 1-pyrrolidinyl, 1-piperidyl, 1-piperazinyl or 1-homopiperazinyl each of which may be substituted by 1 or 2 and same or different substituent(s) selected from a group consisting of phenyl, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, phenyl(C_1-C_6)alkyl, carbamoyl, cyclo(C_3-C_6)alkyl, carboxy, (C_1-C_6)alkynoyl, (C_1-C_6)alkanoylamino, oxo, (C_1-C_6) alkoxycarbonyl and piperidyl;
benzoyl which may be substituted by 1 or 2 and same or different substituent(s) selected from a group consisting of carboxy, cyano, halogen, hydroxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, amino, di(C_1-C_6) alkylamino, (C_1-C_6)alkanoylamino,
(C_1-C_6)alkanesulfonylamino, nitro and
(C_1-C_6)alkoxycarbonyl;
(C_1-C_6)alkanoylamino;
(C_1-C_6)alkoxycarbonylamino;
(C_1-C_6)alkanesulfonylamino;
phenylsulfoylamino;
pyridyl;
indolyl;
phthalimido.

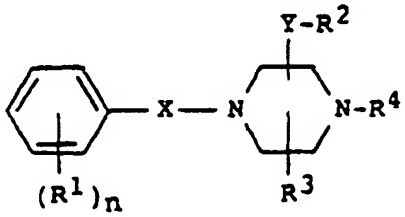
3. The compound of claim 2, which is selected from the group consisting of

(1) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(carbamoylmethyl) piperazine,
(2) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-1H-indol-3-yl-methyl)-4-[(4-cyclohexyl-1-piperazinyl)carbonyl-methyl]piperazine,
(3) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4,1'-bipiperidin-1-yl) carbonylmethyl] piperazine,
(4) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[3-[(4-methyl-1-homopiperazinyl) carbonyl]propyl]piperazine,
(5) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[4-acetylbenzoyl]piperazine and
(6) (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-Indol-3-yl-methyl)-4-[4-(mesylamino)benzoyl]piperazine;

or a pharmaceutically acceptable salt thereof.

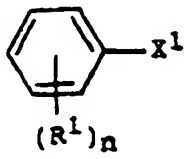
4. The compound of claim 2, which is (2R)-1-[3,5-Bis(trifluoromethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-(4-methyl-1-piperazinyl)carbamoylmethyl]piperazine, or a pharmaceutically acceptable salt thereof.

5. A process for the preparation of a compound of the following general formula:

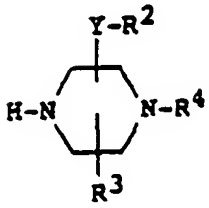


wherein X, Y, R^1, R^2, R^3, R^4 and n are each as defined in claim 1, or its pharmaceutically acceptable salt, which comprises

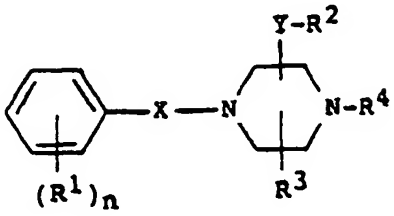
(1) reacting a compound of the formula:



or a salt thereof with a compound of the formula:



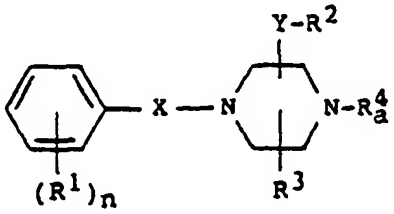
or its reactive derivative at the imino group or a salt thereof to provide a compound of the formula:



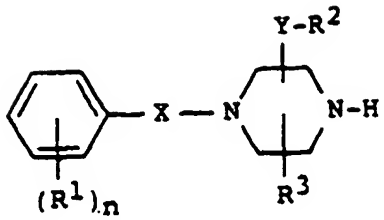
or a salt thereof, in the above formulas,

X, Y, R^1, R^2, R^3, R^4 and n are each as defined above, and
X^1 is a carboxy or its reactive derivative, or a sulfo or its reactive derivative, or

(2) subjecting a compound of the formula:

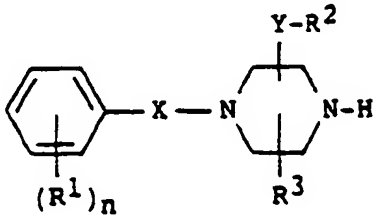


or a salt thereof to an elimination reaction of the imino-protective group to provide a compound of the formula:



or a salt thereof, in the above formulas,
X, Y, R^1, R^2, R^3 and n are each as defined above, and R^4_a is $(C_6\text{-}C_{10})ar(C_1\text{-}C_6)alkyl$, or

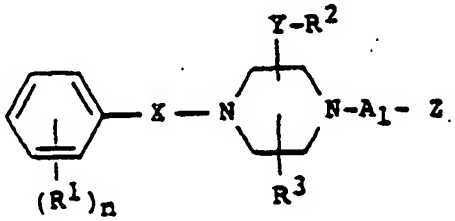
(3) reacting a compound of the formula:



or its reactive derivative at the imino group or a salt thereof with a compound of the formula:

$$W\text{-}A_1\text{-}Z$$

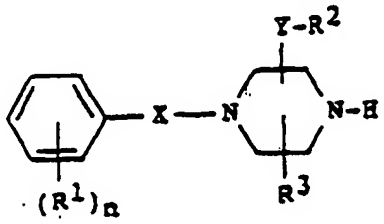
to provide a compound of the formula:



or a salt thereof, in the above formulas,

X, Y, Z, R^1, R^2, R^3, n are each as defined above,
A_1 is $(C_1\text{-}C_6)alkylene$ or $(C_2\text{-}C_6)alkenylene$, and
W is a leaving group, or

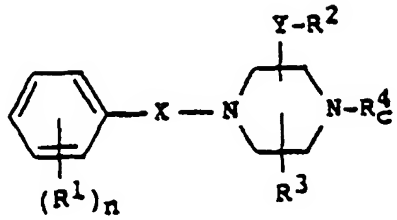
(4) reacting a compound of the formula:



or its reactive derivative at the imino group or a salt thereof with a compound of the formula:

$$X^2\text{-}R^4{}_c$$

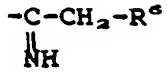
to provide a compound of the formula:



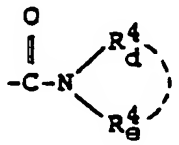
or a salt thereof, in the above formulas,

X, Y, R^1, R^2, R^3 and n are each as defined above,
X^2 is a leaving group, and
$R^4{}_c$ is

(i) a group of the formula $-SO_2-R^5$, in which R^5 is $(C_1\text{-}C_6)$alkyl,
(ii) a group of the formula

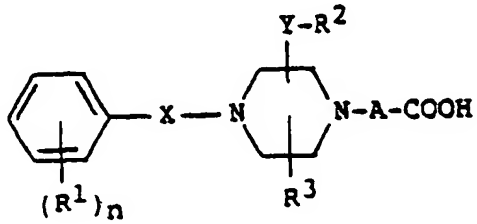


in which R^6 is $(C_1\text{-}C_6)$alkoxy$(C_6\text{-}C_{10})$aryl, or
(iii) carboxy;
$(C_1\text{-}C_6)$alkoxycarbonyl which may be substituted by $C_6\text{-}C_{10}$ aryl;
$(C_1\text{-}C_6)$alkanoyl which may be substituted by a substituent selected from a group consisting of $C_6\text{-}C_{10}$ aryl, halo$(C_6\text{-}C_{10})$aryl, $C_6\text{-}C_{10}$ aryloxy, $(C_1\text{-}C_6)$alkoxy, halogen, amino, di$(C_1\text{-}C_6)$alkylamino, $(C_6\text{-}C_{10})$aroylamino,
cyclo$(C_3\text{-}C_6)$alkyl, and aromatic hetero(mono- or bi-)cyclic group containing one nitrogen atom;
halo$(C_1\text{-}C_6)$alkylcarbonyl;
cyclo$(C_3\text{-}C_6)$alkylcarbonyl;
$(C_2\text{-}C_8)$alkenoyl which may be substituted by a substituent selected from a group consisting of $C_6\text{-}C_{10}$ aryl, dihalo$(C_6\text{-}C_{10})$aryl, $C_6\text{-}C_{10}$ aroyl, cyclo$(C_3\text{-}C_6)$alkyl and aromatic hetero (mono- or bi-)cyclic group containing one nitrogen atom;
$C_6\text{-}C_{10}$ ar$(C_2\text{-}C_6)$alkynoyl;
carbamoyl derivative illustrated by the formula:

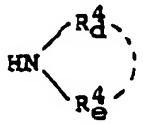


(wherein R^4_d and R^4_e are defined as in claim 1);
C_6-C_{10} aroyl which may be substituted by 1 or 2 and same or different substituent(s) selected from a group consisting of carboxy, cyano, halogen, hydroxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkanoyloxy, amino, di(C_1-C_6)alkylamino, (C_1-C_6)alkanoylamino, (C_1-C_6)alkanesulfonylamino, nitro and (C_1-C_6)alkoxycarbonyl;
aromatic hetero(mono)cyclic carbonyl group containing one or two nitrogen atom(s);
aromatic hereto(bi)cyclic carbonyl group containing one nitrogen or oxygen atom;
saturated heterocyclic carbonyl group containing one nitrogen atom which is substituted by 1 or 2 and same or different substituent(s) selected from a group consisting of hydroxy and (C_1-C_6)alkoxycarbonyl; or

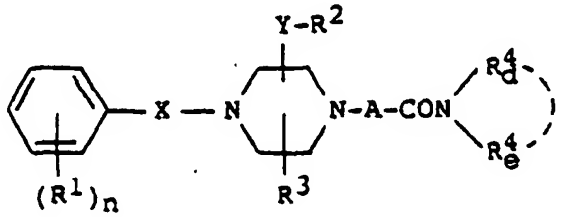
(5) reacting a compound of the formula:



or its reactive derivative at the carboxy group or a salt thereof with a compound of the formula:

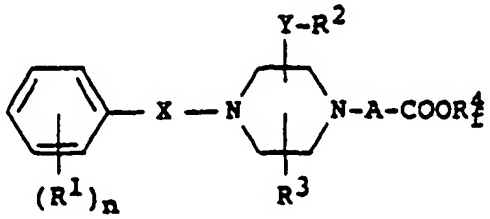


or a salt thereof to provide a compound of the formula:

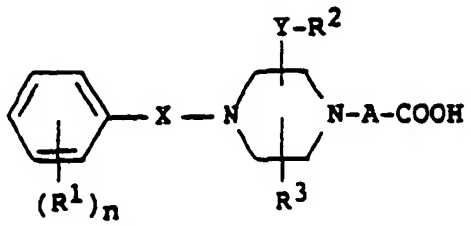


or a salt thereof, in the above formulas,
X, Y, R^1, R^2, R^3, n, A, R^4_d and R^4_e are each as defined above, or

(6) subjecting a compound of the formula:

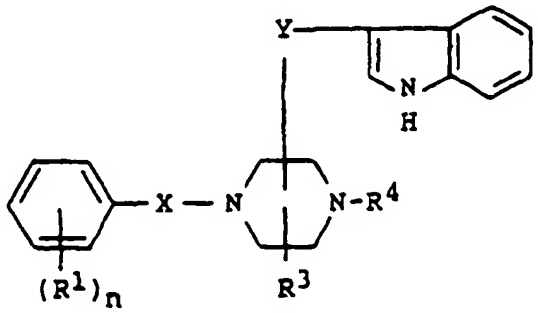


or a salt thereof to a deesterification reaction to provide a compound of the formula:



or a salt thereof, in the above formulas,
X, Y, R^1, R^2, RH, n and A are each as defined above, and R^4_f is $(C_1\text{-}C_6)$alkyl or $(C_6\text{-}C_{10})$ar$(C_1\text{-}C_6)$alkyl, or

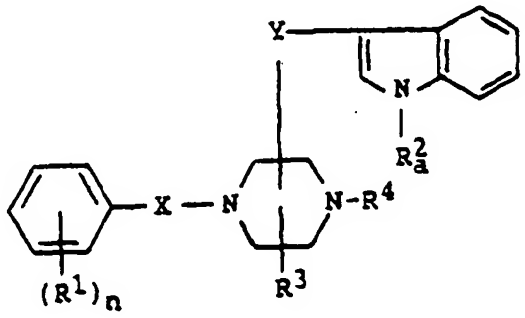
(7) reacting a compound of the formula:



or a salt thereof with a compound of the formula:

$$W\text{-}R^2{}_a$$

to provide a compound of the formula:



or a salt thereof, in the above formulas,
X, Y, W, R^1, R^3, R^4 and n are each as defined above, and $R^2{}_a$ is $(C_1\text{-}C_6)$alkyl.

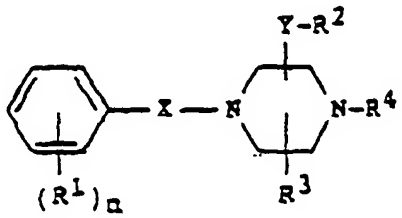
6. A pharmaceutical composition comprising a compound of claim 1 as an active ingredient, in association with a pharmaceutically acceptable, substantially non-toxic carrier or excipient.

7. A compound of claim 1 for use as a medicament.

8. Use of a compound of claim 1 for the manufacture of a medicament for treating or preventing tachykinin-mediated diseases.

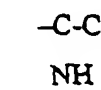
Patentansprüche

1. Verbindung der folgenden allgemeinen Formel:



wobei

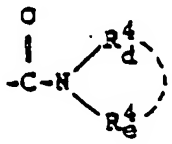
X Carbonyl ist;
Y eine Bindung oder (C_1-C_6)Alkylen ist;
R^1 Halogen, (C_1-C_6)Alkyl, Halo(C_1-C_6)alkyl, C_6-C_{10} Aryloxy, Nitro, Amino, (C_1-C_6)Alkylamino, Di (C_1-C_6)alkylamino, (C_1-C_6)Alkanoylamino oder (C_1-C_6)Alkansulfonylamino ist;
R^2 eine aromatische Hetero(mono- oder bi)cyclische Gruppe ist, die ein Stickstoff- oder Schwefelatom enthält, welche durch einen Substituenten substituiert sein kann, der ausgewählt wird aus der aus (C_1-C_6)Alkyl und Di(C_1-C_6)alkylamino (C_1-C_6)-alkyl bestehenden Gruppe;
R^3 Wasserstoff oder (C_1-C_6)Alkyl ist;
R^4 (i) eine Gruppe der Formel $-SO^2-R^5$ ist, wobei R^5 (C_1-C_6)Alkyl ist
(ii) eine Gruppe der Formel



ist,
wobei R^6 (C_1-C_6)Alkoxy(C_6-C_{10})aryl ist,
oder
(iii) eine Gruppe der Formel -A-Z ist, wobei A eine Bindung, (C_1-C_6)Alkylen oder (C_2-C_6)Alkenylen ist.

Z Wasserstoff;
Nitril;
Amino;
Cyclo(C_3-C_6)alkyl;
(C_1-C_6)Aryl;
C_6-C_{10} Aryloxy;
Carboxy;
(C_1-C_6)Alkoxycarbonyl, welches durch C_6-C_{10} Aryl substituiert sein kann;
(C_1-C_6)Alkanoyl, welches durch einen Substituenten substituiert sein kann,
der ausgewählt wird aus der aus C_6-C_{10} Aryl, Halo(C_6-C_{10})aryl, C_6-C_{10} Aryloxy,
(C_1-C_6)Alkoxy, Halogen, Amino, Di (C_1-C_6)alkylamino,
(C_1-C_6)Aroylamino,
Cyclo(C_3-C_6)alkyl und aromatischer Hetero(mono- oder bi)cyclischer Gruppe,
enthaltend ein Stickstoffatom bestehenden Gruppe;
Halo(C_1-C_6)alkylcarbonyl;
Cyclo (C_3-C_6)alkylcarbonyl;

(C_2-C_6)Alkenoyl, welches durch einen Substituenten substituiert sein kann,
der aus der aus (C_6-C_{10})Aryl, Dihalo(C_6-C_{10})aryl, C_6-C_{10} Aroyl, Cyclo(C_3-C_6)alkyl und aromatischer Hetero (mono- oder bi)cyclischer Gruppe, enthaltend ein Stickstoffatom bestehenden Gruppe ausgewählt wird;
C_6-C_{10} Ar(C_2-C_6)alkinoyl;
durch die Formel



dargestelltes Carbamoylderivat
wobei R^4_d und R^4_e unabhängig voneinander Wasserstoff; (C_1-C_6)Alkyl, welches durch einen Substituenten substituiert sein kann, der aus der aus C_6-C_{10}Aryl, Halo(C_6-C_{10})Aryl, (C_1-C_6)Alkoxy, Hydroxy, Carbamoyl, C_6-C_{10}Ar(C_1-C_6)alkoxycarbonyl, Di(C_1-C_6)Alkylamino, gesättigter heterocyclischer Gruppe, enthaltend ein Stickstoffatom, Carboxy, Cyclo(C_3-C_6)alkyl und aromatischer Hetero(mono)cyclischer Gruppe, enthaltend ein Stickstoffatom bestehenden Gruppe ausgewählt wird; oder gesättigte heterocyclische Gruppe, enthaltend zwei Stickstoffatome, substituiert durch (C_1-C_6)Alkyl sind, oder R^4_d und R^4_e gemeinsam mit dem Stickstoffatom eine gesättigte heterocyclische Gruppe bilden, die ein oder zwei Stickstoffatom(e) enthält, welche durch 1 oder 2 gleiche oder verschiedene Substituent(en) substituiert sein kann, ausgewählt aus der aus C_6-C_{10} Aryl, (C_1-C_6)Alkyl, Hydroxy(C_1-C_6)alkyl, (C_6-C_{10})Ar(C_1-C_6)alkyl, Carbamoyl, Cyclo(C_3-C_6)alkyl, Carboxy(C_1-C_6)alkanoyl, (C_1-C_6)Alkyanoylamino, Oxo, (C_1-C_6)Alkoxycarbonyl, gesättigter heterocyclischer Gruppe, enthaltend ein Stickstoffatom, und aromatischer hetero(mono)cyclischer Gruppe, enthaltend ein Stickstoffatom bestehenden Gruppe;
C_6-C_{10} Aroyl, welches durch 1 oder 2 gleiche oder verschiedene Stubstituent(en) substituiert sein kann, ausgewählt aus einer Gruppe, bestehend aus Carboxy, Cyano, Halogen, Hydroxy, (C_1-C_6)Alkanoyl, (C_1-C_6)Alkanoyloxy, Amino, Di(C_1-C_6)alkylamino, (C_1-C_6)Alkanoylamino, (C_1-C_6)Alkansulfonylamino, Nitro und (C_1-C_6)Alkoxycarbonyl;
aromatische hetero(mono)cyclische Carbonylgruppe, enthaltend ein oder zwei Stickstoffatom(e); aromatische hetero(bi)cyclische Carbonylgruppe, enthaltend 1 Stickstoff- oder Sauerstoffatom; oder gesättigte heterocyclische Carbonylgruppe, enthaltend ein Stickstoffatom, welches durch 1 oder 2 gleiche oder verschiedene Substituent(en) substituiert sein kann, ausgewählt aus der Gruppe, bestehend aus Hydroxy und (C_1-C_6)Alkoxycarbonyl;
(C_1-C_6)Alkanoylamino;
(C_1-C_6)Alkoxycarbonylamino;
(C_1-C_6)Alkansulfonylamino;
C_6-C_{10} Arylsulfonylamino;
hetero(mono- oder bi-)cyclische Gruppe, enthaltend ein Stickstoffatom ist; und

n 0, 1 oder 2 ist;
vorausgesetzt, dass wenn n 2 ist, diese R^1 jeweils gleiche oder verschiedene Gruppen sein können;
oder ihr pharmazeutisch verträgliches Salz.

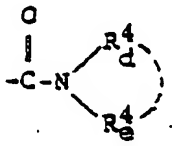
2. Verbindung nach Anspruch 1, wobei

R^1 Halogen, (C_1-C_6)Alkyl, Halo(C_1-C_6)alkyl, Phenyloxy, Nitro, Amino, (C_1-C_6)Alkanoylamino, Di(C_1-C_6)alkylamino, (C_1-C_6)Alkanoylamino, oder (C_1-C_6)Alkansulfonylamino ist;

R^2 Benzothienyl oder Indolyl ist, welches durch einen Substituenten substituiert sein kann, der ausgewählt wird aus der aus (C_1-C_6)Alkyl und Di(C_1-C_6)alkanoylamino(C_1-C_6)alkyl bestehenden Gruppe;

R^4 (i) eine Gruppe der Formel $-SO^2-R^5$ ist, wobei R^5 (C_1-C_6)Alkyl ist
(ii) eine Gruppe der Formel

ist, wobei R^6 (C_1-C_6)Alkoxyphenyl ist, oder
(iii) eine Gruppe der Formel - A - Z ist, wobei A eine Bindung, (C_1-C_6)Alkylen oder (C_2-C_6)Alkenylen ist;
Z Wasserstoff;
Nitril;
Amino;
Cyclo (C_3-C_6)alkyl;
Phenyl;
Phenyloxy;
Carboxy;
(C_1-C_6)Alkoxycarbonyl, das durch Phenyl substituiert sein kann;
(C_1-C_6)Aklanoyl, das durch einen Substituenten substituiert sein kann, der ausgewählt wird aus der aus Phenyl, Halophenyl, Phenyloxy, (C_1-C_6)Alkoxy, Halogen, Amino, Di(C_1-C_6)alkylamino und Benzoylamino bestehenden Gruppe; Cyclo(C_3-C_6)alkyl;
Halo(C_1-C_6)alkylcarbonyl;
Cyclo(C_3-C_6)alkylcarbonyl;
(C_2-C_6)Alkenoyl, das durch einen Substituenten substituiert sein kann, der ausgewählt wird aus der aus Phenyl, Dihalophenyl, Benzoyl und Cyclo(C_3-C_6)alkyl bestehenden Gruppe; Phenyl(C_2-C_6)alkinoyl;
Carbamoylderivat, das durch die folgende Formel



dargestellt wird,
(wobei R^4_d und R^4_e unabhängig voneinander Wasserstoff;
(C_1-C_6)Alkyl, das durch einen Substituenten substituiert sein kann, der ausgewählt wird aus der aus Phenyl, Halophenyl, (C_1-C_6)Alkoxy, Hydroxy, Carbamoyl, Phenyl(C_1-C_6)alkoxycarbonyl, Di(C_1-C_6)alkylamino, Carboxy und Cyclo(C_3-C_6)alkyl bestehenden Gruppe; oder (C_1-C_6)Alkylpiperazinyl sind, oder R^4_d und R^4_e gemeinsam mit dem Stickstofffatom 1-Pyrrolidinyl, 1-Piperidyl, 1-Piperazinyl oder 1-Homopiperazinyl bilden können, von denen jedes durch einen oder zwei gleiche oder verschiedene Substituent(en) substituiert sein kann, die ausgewählt werden aus Phenyl, (C_1-C_6)Alkyl, Hydroxy-(C_1-C_6)alkyl, Phenyl(C_1-C_6)alkyl, Carbamoyl, Cyclo(C_3-C_6)alkyl, Carboxy, (C_1-C_6)Alkinoyl, (C_1-C_6)Alkanoylamino, Oxo, (C_1-C_6)-alkoxycarbonyl und Piperidyl bestehenden Gruppe);
Benzoyl, das durch 1 oder 2 gleiche oder verschiedene Substituent(en) substituiert sein kann, die ausgewählt werden aus der aus Carboxy, Cyano, Halogen, Hydroxy, (C_1-C_6)Alkanoyl, (C_1-C_6)Alkanoyloxy, Amino, Di(C_1-C_6)alkylamino, (C_1-C_6)Alkanoylamino, (C_1-C_6)Alkansulfonyamino, Nitro und (C_1-C_6)Alkoxycarbonyl bestehenden Gruppe;
(C_1-C_6)Alkanoylamino;
(C_1-C_6)Alkoxycarbonylamino;
(C_1-C_6)Alkansulfonylamino;
Phenylsulfoylamino;
Pyridyl;
Indolyl;
Phthalimido ist.

3. Verbindung nach Anspruch 2, welche ausgewählt wird aus der aus

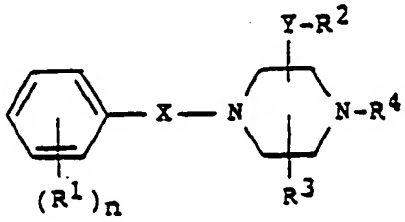
(1) (2R)-1-[3,5-Bis(trifluormethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-(carbamoylmethyl)piperazin,
(2) (2R)-1-[3,5-Bis(trifluormethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4-cyclohexyl-1-piperazinyl)carbonyl-

methyl]piperazin,
(3) (2R)-1-[3,5-Bis(trifluormethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[(4,1'-bipiperidin-1-yl)carbonylmethyl] piperazin,
(4) (2R)-1-[3,5-Bis(trifluormethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[3-[(4-methyl-1-homopiperazinyl)carbonyl]propyl]piperazin,
(5) (2R)-1-[3,5-Bis(trifluormethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[4-acetylbenzoyl]piperazin und
(6) (2R)-1-[3,5-Bis(trifluormethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[4-(mesylamino)benzoyl]piperazin

bestehenden Gruppe; oder ein pharmazeutisch verträgliches Salz davon.

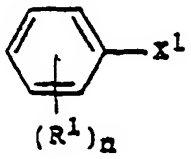
4. Verbindung nach Anspruch 2, welche (2R)-1-[3,5-Bis(trifluormethyl)benzoyl]-2-(1H-indol-3-yl-methyl)-4-[N-(4-methyl-1-piperazinyl)carbamonylmethyl]piperazin oder ein pharmazeutisch verträgliches Salz davon ist.

5. Verfahren zur Herstellung einer Verbindung der folgenden allgemeinen Formel:

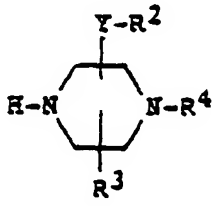


wobei X, Y, R^1, R^2, R^3, R^4 und n jeweils wie in Anspruch 1 definiert sind, oder ihres pharmazeutisch verträglichen Salzes, welches umfasst

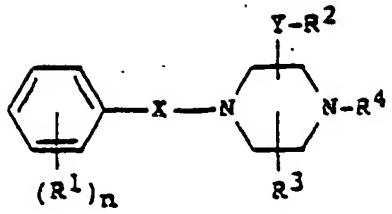
(1) Umsetzung einer Verbindung der Formel:



oder eines Salzes davon mit einer Verbindung der Formel:

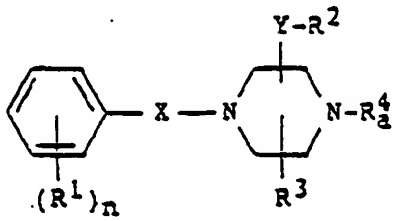


oder ihres reaktiven Derivats an der Imino-Gruppe oder eines Salzes davon zur Herstellung einer Verbindung der Formel:

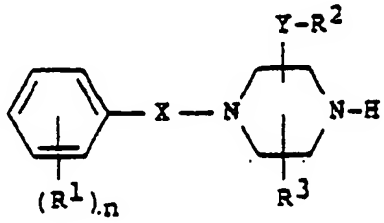


oder eines Salzes davon, wobei in den obigen Formeln X, Y, R^1, R^2, R^3, R^4 und n jeweils wie oben definiert sind, und X^1 Carboxy oder ein reaktives Derivat davon oder Sulfo oder ein reaktives Derivat davon ist, oder

(2) Durchführung einer Eliminierungsreaktion der Imino-Schutzgruppe mit einer Verbindung der Formel:

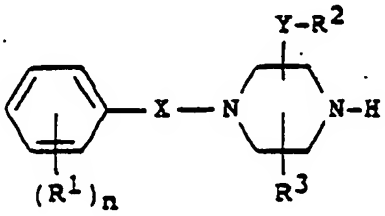


oder eines Salzes davon zur Herstellung einer Verbindung der Formel:



oder eines Salzes davon, wobei in den obigen Formeln
X, Y, R^1, R^2, R^3 und n jeweils wie oben definiert sind, und R^4_a $(C_6\text{-}C_{10})Ar(C_1\text{-}C_6)$alkyl ist, oder

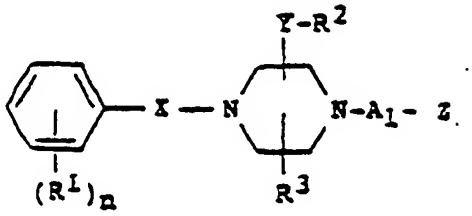
(3) Umsetzung einer Verbindung der Formel:



oder ihres reaktiven Derivats an der Imino-Gruppe oder eines Salzes davon mit einer Verbindung der Formel:

$W\text{-}A_1\text{-}Z$

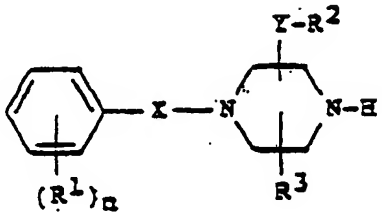
zur Herstellung einer Verbindung der Formel:



oder eines Salzes davon, wobei in den obigen Formeln

X, Y, Z, R^1, R^2, R^3, n jeweils wie oben definiert sind,
A_1 (C_1-C_6)Alkylen oder (C_2-C_6)Alkenylen ist, und
W eine Abgangsgruppe ist, oder

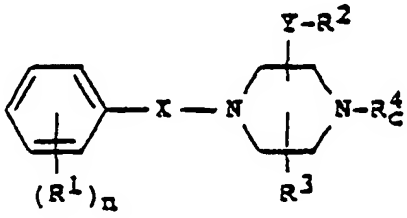
(4) Umsetzung eines Verbindung der Formel:



oder ihres reaktiven Derivats an der Imino-Gruppe oder eines Salzes davon mit einer Verbindung der Formel:

$$X^2\text{-}R^4{}_c$$

zur Herstellung einer Verbindung der Formel :

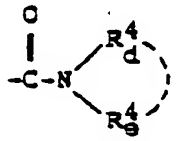


oder eines Salzes davon, wobei in den obigen Formeln

X, Y, R^1, R^2, R^3 und n jeweils wie oben definiert sind,
X^2 eine Abgangsgruppe ist, und
$R^4{}_c$

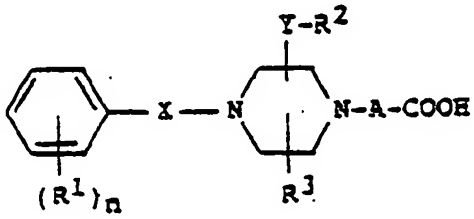
(i) eine Gruppe der Formel -SO_2-R^5,
wobei R^5 (C_1-C_6)Alkyl ist,
(ii) eine Gruppe der Formel

ist, wobei R^6 $(C_1\text{-}C_6)$Alkoxy$(C_6\text{-}C_{10})$aryl ist, oder
(iii) Carboxy;
$(C_1\text{-}C_6)$Alkoxycarbonyl, das durch $C_6\text{-}C_{10}$ Aryl substituiert sein kann;
$(C_1\text{-}C_6)$Alkanoyl, das durch einen Substituenten substituiert sein kann, der ausgewählt wird aus der aus $C_6\text{-}C_{10}$ Aryl, Halo$(C_6\text{-}C_{10})$aryl, $C_6\text{-}C_{10}$ Aryloxy, $(C_1\text{-}C_6)$Alkoxy, Halogen, Amino, Di$(C_1\text{-}C_6)$alkylamino, $(C_6\text{-}C_{10})$Aroylamino,
Cyclo $(C_3\text{-}C_6)$Alkyl, und aromatischer hetero(mono- oder bi-)cyclischer Gruppe, enthaltend 1 Stickstoffatom bestehenden Gruppe;
Halo $(C_1\text{-}C_6)$alkylcarbonyl;
Cyclo $(C_3\text{-}C_6)$alkylcarbonyl;
$(C_2\text{-}C_6)$Alkenoyl, das durch einen Substituenten substituiert sein kann, der aus der aus $C_6\text{-}C_{10}$ Aryl, Dihalo$(C_6\text{-}C_{10})$aryl, $C_6\text{-}C_{10}$ Aroyl, Cyclo $(C_3\text{-}C_6)$Alkyl und aromatischer hetero(mono- oder bi-)cyclischer Gruppe, enthaltend ein Stickstoffatom bestehenden Gruppe ausgewählt wird;
$C_6\text{-}C_{10}$ Ar $(C_2\text{-}C_6)$alkinoyl;
Carbamoylderivat, dargestellt durch die Formel



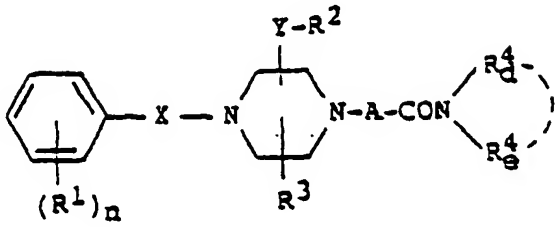
(wobei $R^4{}_d$ und $R^4{}_e$ wie in Anspruch 1 definiert sind);
$C_6\text{-}C_{10}$ Aroyl, das durch 1 oder 2 gleiche oder verschiedene Substituent(en) substituiert sein kann, die ausgewählt werden aus der aus Carboxy, Cyano, Halogen, Hydroxy, $(C_1\text{-}C_6)$Alkanoyl, $(C_1\text{-}C_6)$Alkanoyloxy, Amino, Di$(C_1\text{-}C_6)$alkylamino, $(C_1\text{-}C_6)$Alkanoylamino, $(C_1\text{-}C_6)$Alkansulfonylamino, Nitro und $(C_1\text{-}C_6)$Alkoxycarbonyl bestehenden Gruppe;
aromatische hetero(mono)cyclische Carbonyl-Gruppe, enthaltend ein oder zwei Stickstoffatom(e);
aromatische hetero(bi)cyclische Carbonyl-Gruppe, enthaltend ein Stickstoff- oder Sauerstoffatom;
gesättigte heterocyclische Carbonyl-Gruppe, enthaltend ein Stickstoffatom, welche substituiert ist durch 1 oder 2 gleiche oder verschiedene Substituent(en), ausgewählt aus der aus Hydroxy und $(C_1\text{-}C_6)$Alkoxycarbonyl bestehenden Gruppe ist; oder

(5) Umsetzung einer Verbindung der Formel:



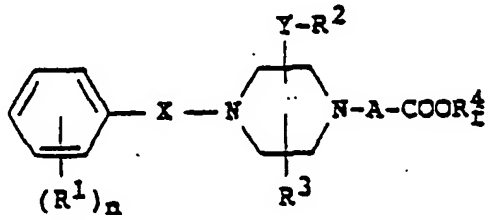
oder ihres reaktiven Derivats an der Carboxy-Gruppe oder eines Salzes davon mit einer Verbindung der Formel:

oder eines Salzes davon zur Herstellung einer Verbindung der Formel:

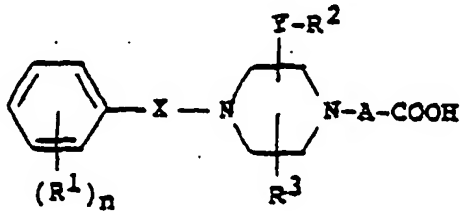


oder eines Salzes davon, wobei in den obigen Formeln
X, Y, R^1, R^2, R^3, n, A, $R^4{}_d$ und $R^4{}_e$ jeweils wie oben definiert sind, oder

(6) Durchführung einer Esterspaltungsreaktion mit einer Verbindung der Formel:



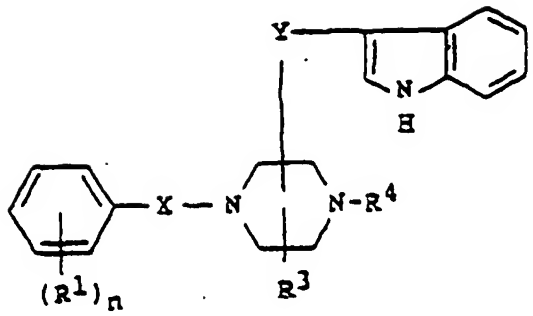
oder eines Salzes davon zur Herstellung einer Verbindung der Formel



oder eines Salzes davon, wobei in den obigen Formeln

X, Y, R^1, R^2, RH, n und A jeweils wie oben definiert sind, und
$R^4{}_f$ (C_1-C_6)Alkyl oder (C_6-C_{10})ar (C_1-C_6)Alkyl ist, oder

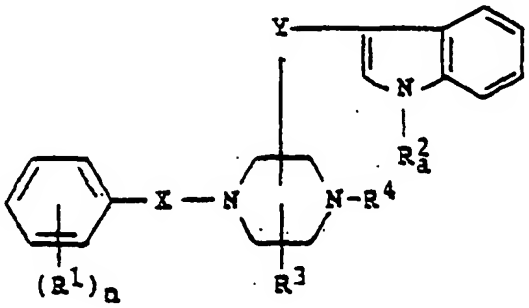
(7) Umsetzung einer Verbindung der Formel:



oder eines Salzes davon mit der Verbindung der Formel:

$$W\text{-}R^2{}_a$$

zur Herstellung einer Verbindung der Formel :



oder eines Salzes davon, wobei in den obigen Formeln

X, Y, W, R^1, R^3, R^4 und n jeweils wie oben definiert sind, und
$R^2{}_a$ (C_1-C_6)Alkyl ist.

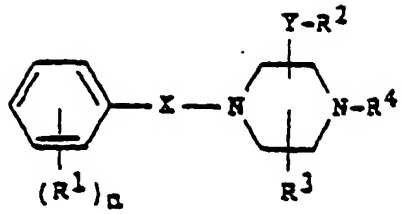
6. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach Anspruch 1 als aktiven Bestandteil in Verbindung mit einem pharmazeutisch verträglichen, im wesentlichen nicht-toxischen Träger oder Exzipienten.

7. Verbindung nach Anspruch 1 zur Verwendung als Medikament.

8. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung eines Medikaments zur Behandlung oder Vorbeugung von Tachykinin-vermittelten Erkrankungen.

Revendications

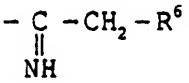
1. Composé de formule générale suivante :



dans laquelle

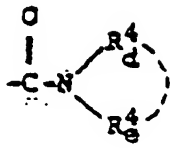
X est un carbonyle,
Y est une liaison ou un alkylène (en C_1-C_6),
R^1 est un halogène, un alkyle (en C_1-C_6), un halogénoalkyle (en C_1-C_6), un aryloxy (en C_6-C_{10}), un nitro, un amino, un alkylamino (en C_1-C_6), un dialkylamino (en C_1-C_6), un alcanoylamino (en C_1-C_6) ou un alcanesulfonylamino (en C_1-C_6),
R^2 est un groupement mono- ou bi-hétérocyclique aromatique contenant un atome d'azote ou de soufre qui peut être substitué par un substituant choisi parmi un groupe constitué d'un alkyle (en C_1-C_6) et d'un dialkylamino (en C_1-C_6) alkyle (en C_1-C_6),
R^3 est un hydrogène ou un alkyle (en C_1-C_6),
R^4 est

(i) un groupement de formule $-SO_2-R^5$ dans laquelle R^5 est un alkyle (en C_1-C_6)
(ii) un groupement de formule



dans laquelle R^6 est un alcoxy (en C_1-C_6) aryle (en C_6-C_{10}), ou
(iii) un groupement de formule -A-Z, dans laquelle

A est une liaison, un alkylène (en C_1-C_6) ou un alcénylène (en C_2-C_6),
Z est un hydrogène,
un nitrile,
un amino,
un cycloalkyle (en C_3-C_6),
un aryle (en C_1-C_6),
un aryloxy (en C_6-C_{10}),
un carboxy,
un alcoxycarbonyle (en C_1-C_6) qui peut être substitué par un aryle (en C_6-C_{10}),
un alcanoyle (en C_1-C_6) qui peut être substitué par un substituant choisi parmi un groupe constitué d'un aryle (en C_6-C_{10}), un halogénoaryle (en C_6-C_{10}), un aryloxy (en C_6-C_{10}), un alcoxy (en C_1-C_6), un halogène, un amino, un dialkylamino (en C_1-C_6),
un aroylamino (en C_1-C_6),
un cycloalkyle (en C_3-C_6), et un groupement mono- ou bi-hétérocyclique aromatique contenant un atome d'azote,
un halogénoalkylcarbonyle (en C_1-C_6),
un cycloalkylcarbonyle (en C_3-C_6),
un alcénoyle (en C_2-C_6) qui peut être substitué par un substituant choisi parmi un groupe constitué d'un aryle (en C_6-C_{10}), un dihalogénoaryle (en C_6-C_{10}), un aroyle (en C_6-C_{10}), un cycloalkyle (en C_3-C_6) et un groupement mono- ou bi-hétérocyclique aromatique contenant un atome d'azote,
un ar (en C_6-C_{10}) alcynoyle (en C_2-C_6),
un dérivé carbamoyle représenté par la formule



(dans laquelle R^4_d et R^4_e sont indépendamment un hydrogène, un alkyle (en C_1-C_6) qui peut être substitué par un substituant choisi parmi un groupe constitué d'un aryle (en C_6-C_{10}), un halogénoaryle (en C_6-C_{10}), un alcoxy (en C_1-C_6), un hydroxy, un carbamoyle, un ar (en C_6-C_{10}) alcoxycarbonyle (en C_1-C_6), un dialkylamino (en C_1-C_6), un groupement hétérocyclique saturé contenant un atome d'azote, un carboxy, un cycloalkyle (en C_3-C_6) et un groupement mono-hétérocyclique aromatique contenant un atome d'azote, ou un groupement hétérocyclique saturé contenant deux atomes d'azote substitué par un alkyle (en C_1-C_6), ou bien R^4_d et R^4_e en même temps que l'atome d'azote forment un groupement hétérocyclique saturé contenant un ou deux atomes d'azote qui peut être substitué par 1 ou 2 substituants identiques ou différents choisis parmi un groupe constitué d'un aryle (en C_6-C_{10}), un alkyle (en C_1-C_6), un hydroxyalkyle (en C_1-C_6), un ar (en C_6-C_{10}) alkyle (en C_1-C_6), un carbamoyle, un cycloalkyle (en C_3-C_6), un carboxyalcanoyle (en C_1-C_6), un alcanoylamino (en C_1-C_6), un oxo, un alcoxycarbonyle (en C_1-C_6), un groupement hétérocyclique saturé contenant un atome d'azote et un groupement mono-hétérocyclique aromatique contenant un atome d'azote, un aroyle (en C_6-C_{10}) qui peut être substitué par 1 ou 2 substituants identiques ou différents choisis parmi un groupe constitué d'un carboxy, un cyano, un halogène, un hydroxy, un alcanoyle (en C_1-C_6), un alcanoyloxy (en C_1-C_6), un amino, un dialkylamino (en C_1-C_6), un alcanoylamino (en C_1-C_6), un alcanesulfonylamino (en C_1-C_6), un nitro et un alcoxycarbonyle (en C_1-C_6),
un groupement carbonyle mono-hétérocyclique aromatique contenant un ou deux atomes d'azote, un groupement carbonyle bi-hétérocyclique aromatique contenant un atome d'azote ou un atome d'oxygène, ou un groupement carbonyle hétérocyclique saturé contenant un atome d'azote qui est substitué par 1 ou 2 substituants identiques ou différents choisis parmi un groupe constitué d'un hydroxy et d'un alcoxycarbonyle (en C_1-C_6),
un alcanoylamino (en C_1-C_6),
un alcoxycarbonylamino (en C_1-C_6),
un alcanesulfonylamino (en C_1-C_6),
un arylsulfonylamino (en C_6-C_{10}),
un groupement mono- ou bi-hétérocyclique aromatique contenant un atome d'azote,
et

n est 0, 1, ou 2, dans la mesure où lorsque n est 2, ces R^1 peuvent être des groupements identiques ou différents respectivement,
ou son sel pharmaceutiquement acceptable.

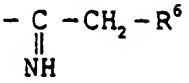
2. Composé selon la revendication 1, dans lequel

R^1 est un halogène, un alkyle (en C_1-C_6), un halogénoalkyle (en C_1-C_6), un phényloxy, un nitro, un amino, un alcanoylamino (en C_1-C_6), un dialkylamino (en C_1-C_6), un alcanoylamino (en C_1-C_6) ou un alcanesulfonylamino (en C_1-C_6),

R^2 est un benzothiényle ou un indolyle qui peut être substitué par un substituant choisi parmi un groupe constitué d'un alkyle (en C_1-C_6) et
d'un dialkylamino (en C_1-C_6) alkyle (en C_1-C_6),

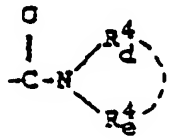
R^4 est

(i) un groupement de formule $-SO_2-R^5$ dans laquelle R^5 est un alkyle (en C_1-C_6)
(ii) un groupement de formule



dans laquelle R^6 est un alcoxyphényle (en C_1-C_6), ou
(iii) un groupement de formule -A-Z
dans laquelle,

A est une liaison, un alkylène (en C_1-C_6) ou un alcénylène (en C_2-C_6),
Z est un hydrogène,
un nitrile,
un amino,
un cycloalkyle (en C_3-C_6),
un phényle,
un phényloxy,
un carboxy,
un alcoxycarbonyle (en C_1-C_6), qui peut être substitué par un phényle,
un alcanoyle (en C_1-C_6) qui peut être substitué par un substituant choisi parmi un groupe constitué d'un phényle, un halogénophényle, un phényloxy, un alcoxy (en C_1-C_6), un halogène, un amino, un dialkylamino (en C_1-C_6), et
un benzoylamino,
un cycloalkyle (en C_3-C_6),
un halogénoalkylcarbonyle (en C_1-C_6),
un cycloalkylcarbonyle (en C_3-C_6),
un alcénoyle (en C_2-C_6) qui peut être substitué par un substituant choisi parmi un groupe constitué d'un phényle, un dihalogénophényle, un benzoyle et un cycloalkyle (en C_3-C_6),
un phénylalcynoyle (en C_2-C_6),
un dérivé carbamoyle représenté par la formule :



(dans laquelle $R^4{}_d$ et $R^4{}_e$ sont indépendamment un hydrogène, un alkyle (en C_1-C_6) qui peut être substitué par un substituant choisi parmi un groupe constitué d'un phényle, un halogénophényle, un alcoxy (en C_1-C_6), un hydroxy, un carbamoyle, un phénylalcoxycarbonyle (en C_1-C_6), un dialkylamino (en C_1-C_6), un carboxy et un cycloalkyle (en C_3-C_6), ou un alkyl (en C_1-C_6) pipérazinyle, ou bien $R^4{}_d$ et $R^4{}_e$ en même temps que l'atome d'azote forment un 1-pyrrolidinyle, un 1-pipéridyle, un 1-pipérazinyle ou un 1-homopipérazinyle, dont chacun peut être substitué par 1 ou 2 substituants identiques ou différents choisis parmi un groupe constitué d'un phényle, un alkyle (en C_1-C_6), un hydroxyalkyle (en C_1-C_6), un phénylalkyle (en C_1-C_6), un carbamoyle, un cycloalkyle (en C_3-C_6), un carboxy, un alcynoyle (en C_1-C_6), un alcanoylamino (en C_1-C_6), un oxo, un alcoxycarbonyle (en C_1-C_6) et un pipéridyle,
un benzoyle qui peut être substitué par 1 ou 2 substituants identiques ou différents choisis parmi un groupe constitué d'un carboxy, un cyano, un halogène, un hydroxy, un alcanoyle (en C_1-C_6), un alcanoyloxy (en C_1-C_6), un amino, un dialkylamino (en C_1-C_6), un alcanoylamino (en C_1-C_6), un alcanesulfonylamino (en C_1-C_6), un nitro et
un alcoxycarbonyle (en C_1-C_6),
un alcanoylamino (en C_1-C_6),
un alcoxycarbonylamino (en C_1-C_6),
un alcanesulfonylamino (en C_1-C_6),
un phénylsulfonylamino,
un pyridyle,
un indolyle,

un phtalimido.

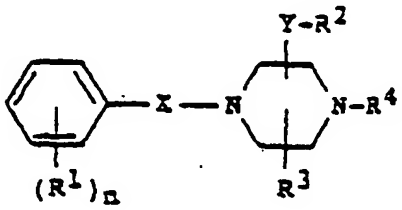
3. Composé selon la revendication 2, lequel est choisi parmi le groupe constitué de

(1) la (2R)-1-[3,5-Bis(trifluorométhyl)benzoyl]-2-(1H-indol-3-yl-méthyl)-4-(carbamoylméthyl)pipérazine,
(2) la (2R)-1-[3,5-Bis(trifluorométhyl)benzoyl]-2-(1H-indol-3-yl-méthyl)-4-[(4-cyclohexyl-1-pipérazinyl)carbonylméthyl]pipérazine,
(3) la (2R)-1-[3,5-Bis(trifluorométhyl)benzoyl]-2-(1H-indol-3-yl-méthyl)-4-[(4-1'-bipipéridine-1-yl)carbonylméthyl]pipérazine,
(4) la (2R)-1-[3,5-Bis(trifluorométhyl)benzoyl]-2-(1H-indol-3-yl-méthyl)-4-[3-[(4-méthyl-1-homopipérazinyl) carbonyl]propyl]pipérazine,
(5) la (2R)-1-[3,5-Bis(trifluorométhyl)benzoyl]-2-(1H-indol-3-yl-méthyl)-4-[4-acétylbenzoyl]pipérazine, et
(6) la (2R)-1-[3,5-Bis(trifluorométhyl)benzoyl]-2-(1H-indol-3-yl-méthyl)-4-[4-(mésylamino)benzoyl]pipérazine

ou d'un sel pharmaceutiquement acceptable de celles-ci.

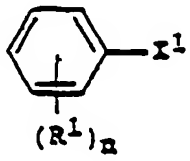
4. Composé selon la revendication 2, qui est la (2R)-1-[3,5-Bis(trifluorométhyl)benzoyl]-2-(1H-indol-3-yl-méthyl)-4-[N-(4-méthyl-1-pipérazinyl)carbamoylméthyl]pipérazine, ou un sel pharmaceutiquement acceptable de celle-ci.

5. Procédé pour la préparation d'un composé de formule générale suivante :

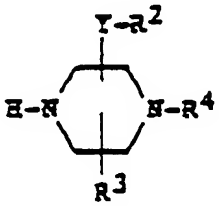


dans laquelle X, Y, R^1, R^2, R^3, R^4 et n sont chacun tels que définis dans la revendication 1, ou de son sel pharmaceutiquement acceptable, qui comprend

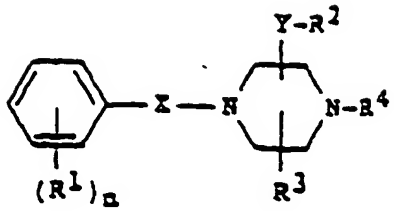
(1) la réaction d'un composé de formule :



ou d'un sel de celui-ci avec un composé de formule :

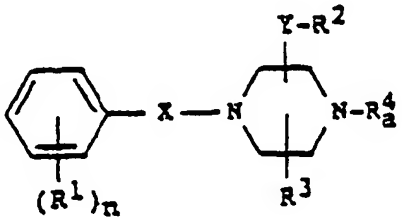


ou son dérivé réactif au niveau du groupement imino ou un sel de celui-ci afin de fournir un composé de formule :

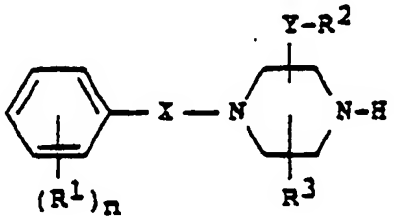


ou un sel de celui-ci, dans les formules ci-dessus,
X, Y, R^1, R^2, R^3, R^4 et n sont chacun tels que définis ci-dessus, et X^1 est un carboxy ou son dérivé réactif, ou un sulfo ou son dérivé réactif, ou

(2) l'exposition d'un composé de formule :

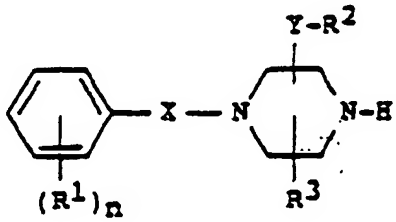


ou d'un sel de celui-ci à une réaction d'élimination du groupement imino-protecteur afin de fournir un composé de formule :



ou un sel de celui-ci, dans les formules ci-dessus,
X, Y, R^1, R^2, R^3 et n sont chacun tels que définis ci-dessus, et R^4_a est un ar (en C_6-C_{10}) alkyle (en C_1-C_6), ou bien

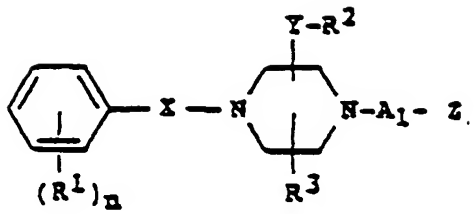
(3) la réaction d'un composé de formule :



ou de son dérivé réactif au niveau du groupement imino ou d'un sel de celui-ci avec un composé de formule :

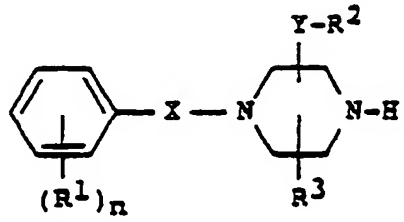
$$W\text{-}A_1\text{-}Z$$

pour fournir un composé de formule :



ou un sel de celui-ci, dans les formules ci-dessus,
X, Y, Z, R^1, R^2, R^3, n sont chacun tels que définis ci-dessus, A_1 est un alkylène (en C_1-C_6) ou un alcénylène (en C_2-C_6), et W est un groupement nucléofuge, ou bien

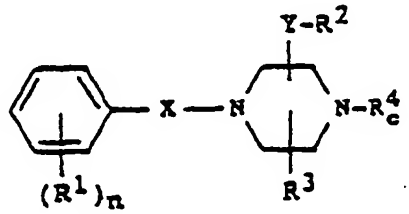
(4) la réaction d'un composé de formule :



ou de son dérivé réactif au niveau du groupement imino ou d'un sel de celui-ci avec un composé de formule :

$$X^2\text{-}R^4{}_c$$

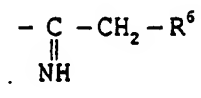
pour fournir un composé de formule :



ou un sel de celui-ci, dans les formules ci-dessus,

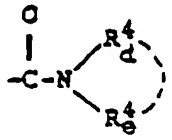
X, Y, R^1, R^2, R^3 et n sont chacun tels que définis ci-dessus,
X^2 est un groupement nucléofuge, et
$R^4{}_c$ est

(i) un groupement de formule $-SO_2-R^5$ dans laquelle R^5 est un alkyle (en C_1-C_6)
(ii) un groupement de formule



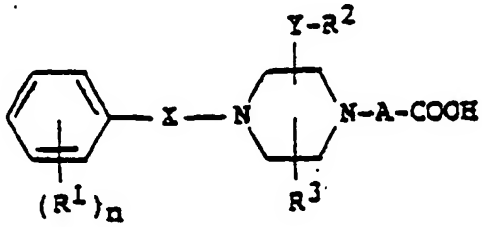
dans laquelle R^6 est un alcoxy (en C_1-C_6) aryle (en C_6-C_{10}), ou
(iii) un carboxy,
un alcoxycarbonyle (en C_1-C_6) qui peut être substitué par un aryle (en C_6-C_{10}), un alcanoyle (en C_1-C_6) qui peut être substitué par un substituant choisi parmi un groupe constitué d'un aryle (en C_6-C_{10}), un halogénoaryle (en C_6-C_{10}), un aryloxy (en C_6-C_{10}), un alcoxy (en C_1-C_6), un halogène, un amino,

un dialkylamino (en C_1-C_6), un aroylamino (en C_6-C_{10})
un cycloalkyle (en C_3-C_6), et un groupement mono- ou bi-hétérocyclique aromatique contenant un atome d'azote,
un halogénoalkylcarbonyle (en C_1-C_6),
un cycloalkylcarbonyle (en C_3-C_6),
un alcénoyle (en C_2-C_6) qui peut être substitué par un substituant choisi parmi un groupe constitué d'un aryle (en C_6-C_{10}), un dihalogénoaryle (en C_6-C_{10}), un aroyle (en C_6-C_{10}), un cycloalkyle (en C_3-C_6) et un groupement mono- ou bi-hétérocyclique aromatique contenant un atome d'azote,
un ar (en C_6-C_{10}) alcynoyle (en C_2-C_6),
un dérivé carbamoyle représenté par la formule

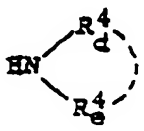


(dans laquelle R^4_d et R^4_e sont définis comme dans la revendication 1),
un aroyle (en C_6-C_{10}) qui peut être substitué par 1 ou 2 substituants identiques ou différents choisis parmi un groupe constitué d'un carboxy, un cyano, un halogène, un hydroxy, un alcanoyle (en C_1-C_6), un alcanoyloxy (en C_1-C_6), un amino, un dialkylamino (en C_1-C_6), un alcanoylamino (en C_1-C_6), un alcanesulfonylamino (en C_1-C_6), un nitro et un alcoxycarbonyle (en C_1-C_6),
un groupement carbonyle mono-hétérocyclique aromatique contenant un ou deux atomes d'azote,
un groupement carbonyle bi-hétérocyclique aromatique contenant un atome d'azote ou un atome d'oxygène,
un groupement carbonyle hétérocyclique saturé contenant un atome d'azote qui est substitué par 1 ou 2 substituants identiques ou différents choisis parmi un groupe constitué d'un hydroxy et d'un alcoxycarbonyle (en C_1-C_6), ou

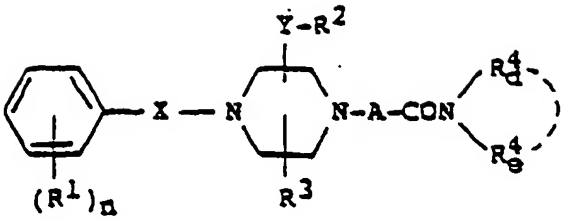
(5) la réaction d'un composé de formule :



ou de son dérivé réactif au niveau du groupement carboxy ou d'ur sel de celui-ci avec un composé de formule :

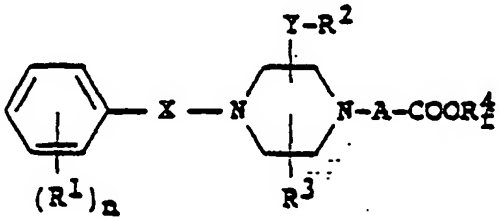


ou un sel de celui-ci afin d'obtenir un composé de formule :

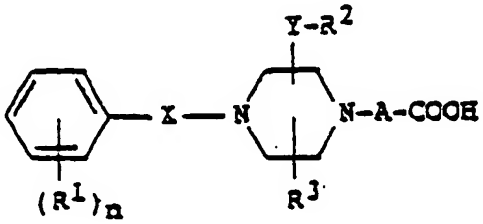


ou un sel de celui-ci, dans les formules ci-dessus,
X, Y, R^1, R^2, R^3, n, A, $R^4{}_d$ et $R^4{}_e$ sont chacun tels que définis ci-dessus, ou

(6) l'exposition d'un composé de formule :

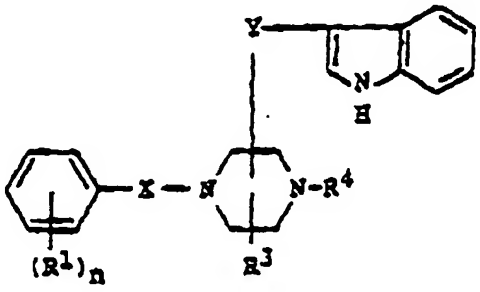


ou d'un sel de celui-ci à une réaction de désestérification afin d'obtenir un composé de formule :



ou un sel de celui-ci, dans les formules ci-dessus,
X, Y, R^1, R^2, RH, n et A sont chacun tels que définis ci-dessus, et $R^4{}_f$ est un alkyle (en C_1-C_6) ou un ar (en C_6-C_{10}) alkyle (en C_1-C_6), ou

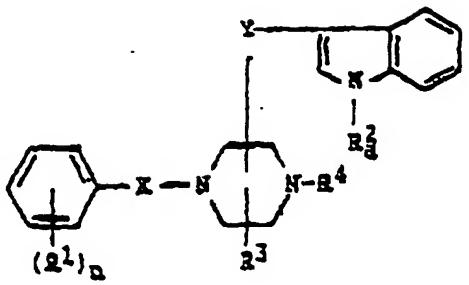
(7) la réaction d'un composé de formule :



ou d'un sel de celui-ci avec un composé de formule :

$$W\text{-}R^2{}_a$$

pour fournir un composé de formule :



ou un sel de celui-ci, dans les formules ci-dessus,
X, Y, W, R^1, R^3, R^4 et n sont chacun tels que définis ci-dessus, et $R^2{}_a$ est un alkyle (en C_1-C_6).

6. Composition pharmaceutique comprenant un composé selon la revendication 1 en tant que principe actif, en association avec un support ou excipient pharmaceutiquement acceptable, substantiellement non toxique.

7. Composé selon la revendication 1 destiné à une utilisation en tant que médicament.

8. Utilisation d'un composé selon la revendication 1 pour la fabrication d'un médicament destiné à traiter ou prévenir des maladies médiées par la tachykinine.